Original Article

Efficacy and safety of trifluridine/tipiracil plus bevacizumab versus trifluridine/tipiracil monotherapy for refractory metastatic colorectal cancer: a retrospective cohort study

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Background: Several studies demonstrated trifluridine/tipiracil (TAS-102) plus bevacizumab (BEV) had better efficacy than the monotherapy of TAS-102 in refractory metastatic colorectal cancer (mCRC). However, it remains unclear whether Chinese population can benefit from this combination or not. Hence, we conducted this retrospective cohort study to compare the efficacy and safety between TAS-102 plus BEV with TAS-102 monotherapy in refractory mCRC.

Methods: This retrospective cohort study enrolled patients (any age) with refractory mCRC from Hunan Cancer Hospital. The main inclusion criteria were histopathologically and/or radiographically confirmed refractory mCRC, World Health Organization (WHO) performance status of 0 to 2, adequate organ function, and initial treatment of TAS-102 with or without BEV between November 2020 and October 2022. Previous therapy with fruquintinib or regorafenib was allowed but not mandatory. Baseline demographic and clinical characteristics were collected appropriately. Every 2 or 3 treatment cycles, the patients were assessed by computed tomography (CT) scans and clinical assessments until disease progression or loss to follow-up. The National Cancer Institute Common Terminology Criteria for Adverse Events 5.0 (NCI-CTCAE 5.0) were presented as n (%). The primary endpoint was investigator-evaluated overall survival (OS). As this is a retrospective cohort study, sample size calculation was not performed. Eligible patients would be enrolled as many as possible.

Results: A total of 90 patients were enrolled, including 58 patients who received TAS-102 plus BEV and another 32 patients who received TAS-102 monotherapy. The known baseline characteristics were comparable (P<0.05). With a median follow-up of 4.60 months (range, 0.20–22.80), the median OS (mOS) time in the TAS-102 plus BEV group was longer than that in the TAS-102 monotherapy group (10.83 *vs.* 7.43 months), but the difference was not significant (P=0.79). The median progression-free survival (mPFS) time was comparable between the two groups (4.67 *vs.* 4.30 months, P=0.96). Multivariate Cox regression analysis demonstrated that undergoing therapy after TAS-102 either with or without BEV was an independent risk factor for OS [hazard ratio (HR) =0.25; 95% confidence interval (CI): 0.09–0.71, P<0.01], and previous treatment with cetuximab was an independent protective factor for PFS (HR =0.17; 95% CI: 0.03–0.91, P=0.04). Of the 70 patients who were evaluated, those receiving TAS-102 plus BEV showed trend

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of a higher objective response rate (ORR) and disease control rate (DCR) than those who received TAS-102 monotherapy (P=0.16 and P=0.29, respectively). Adverse events (AEs) were similar between the two groups, except that the incidence of platelet count decrease (grade ≥3) was significantly higher in the TAS-102 plus BEV group.

Conclusions: There was a trend in favor of the combination of BEV plus TAS-102 regarding OS and DCR, without reaching statistical significance, and it means that there was no clear advantage of one over the other in terms of efficacy. Further prospective studies are still necessary to draw a definite conclusion.

Keywords: Colorectal cancer (CRC); trifluridine/tipiracil (TAS-102); bevacizumab (BEV)

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Introduction

Colorectal cancer (CRC) is the 3rd most common cancer and the 2nd most lethal cancer worldwide (1). Standard treatment of patients who have metastatic CRC (mCRC) includes oxaliplatin-containing therapy. It is followed by irinotecan-containing therapy at progression (or the opposite sequence) and also combined with epidermal growth factor receptor (EGFR)-targeted antibodies (e.g., cetuximab or panitumumab) in patients with left-sided *RAS* wild-type tumors, or antiangiogenic antibodies [e.g., bevacizumab (BEV), ramucirumab, or aflibercept] in patients who develop right-sided or *RAS*-mutation upon first- and second-line therapy (2). For the first-line treatment, the objective response rate (ORR) of mCRC is roughly 50% whereas for the second-line treatment, it decreases to 10–20%. In third-line treatment, for refractory mCRC, chemotherapeutic drugs hardly have an effect, and it is difficult to shrink the tumor (3). At present, the third-line treatments suggested by guidelines for mCRC include regorafenib, fruquintinib, and trifluridine/tipiracil (TAS-102) (4-8).

TAS-102 is a new oral cytotoxic chemotherapy medicine consisting of trifuridine (FTD) and tipiracil hydrochloride. FTD is an active cytotoxic element, the triphosphate form of which is integrated into DNA to result in its antitumor effects (9). Tipiracil hydrochloride is a strong inhibitor of thymidine phosphorylase (TP), which acts in a synergistic manner with anti-vascular endothelial growth factor (VEGF) targeted treatment to prevent tumor angiogenesis and inhibits the fast degradation of the trifluridine (10,11). The phase III trials RECOURSE and TERRA showed that TAS-102 notably increased the overall survival (OS) and progression-free survival (PFS) of mCRC and presented a manageable safety profile (12,13). However, their survival benefits are modest and require augmentation. The perfect safety profile of TAS-102 has stimulated the investigation of other options for the therapy of mCRC combined with other agents (14). TAS-102 plus BEV have shown encouraging prognosis in several recent studies of mCRC (15-18). Moreover, the phase 3 SUNLIGHT trial revealed that TAS-102 plus BEV promoted the clinical outcomes of patients with refractory mCRC compared with TAS-102 monotherapy (19).

Highlight box

Key findings

- Compared with trifluridine/tipiracil (TAS-102) monotherapy, TAS-102 plus bevacizumab (BEV) seemed to have comparable safety and a trend of improved disease control and prognosis in the Chinese patients with refractory metastatic colorectal cancer (mCRC).

What is known and what is new?

- Several studies showed that TAS-102 plus BEV demonstrated better prognosis than TAS-102 monotherapy in mCRC.
- We found there was the same trend in favor of the combination of BEV plus TAS-102 regarding overall survival (OS) and disease control rate, though not reaching statistical significance in Chinese population; In addition, undergoing therapy after TAS-102 either with or without BEV was an independent risk factor for OS and previous treatment with cetuximab was an independent protective factor for progression-free survival.

What is the implication, and what should change now?

- Further prospective studies are still needed to confirm that TAS-102 plus BEV can improve disease control and prognosis in patients with refractory mCRC.

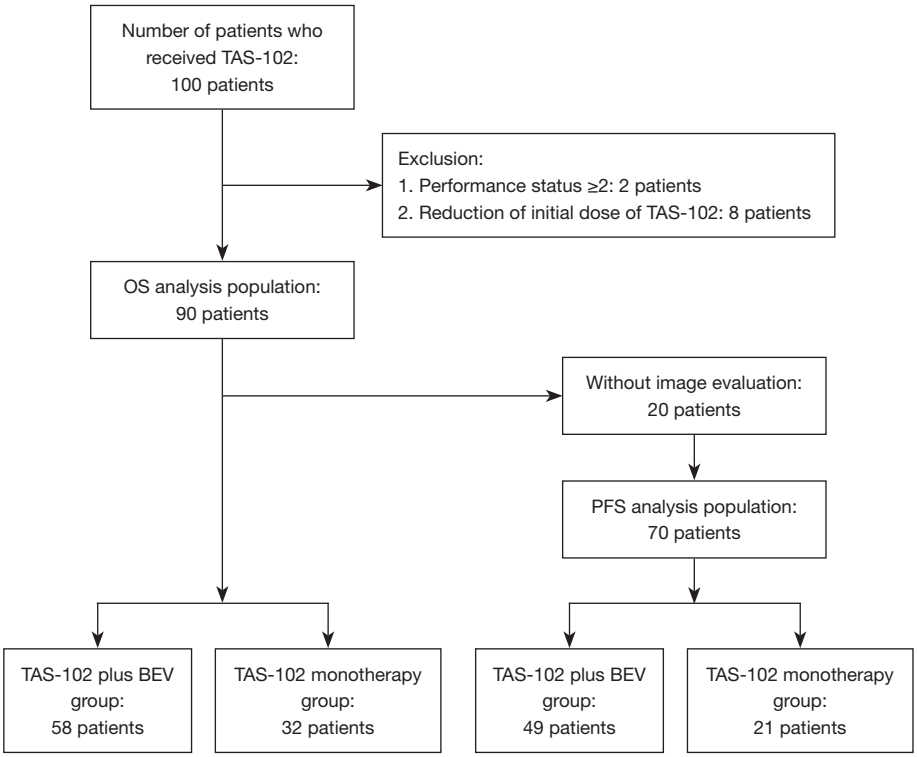

Figure 1 Flow diagram. TAS-102, trifluridine/tipiracil; BEV, bevacizumab; OS, overall survival; PFS, progression-free survival.

However, it remains unclear whether the combination therapy can provide extra benefit to the Chinese population or not. Hence, this retrospective cohort study was designed to assess the efficacy and safety TAS-102 plus BEV as compared with TAS-102 alone in Chinese patients with refractory mCRC. We present this article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-98/rc).

Methods

Study design and patients

A retrospective analysis was conducted to explore the efficacy and safety of patients treated with at least 1 cycle of TAS-102 with or without BEV in patients with refractory mCRC from November 2020 to October 2022 at the Hunan Cancer Hospital. Data were collected from the institutional electronic medical records. The median OS (mOS) was the primary endpoint, whereas mPFS, ORR, disease control rate (DCR), and the incidence of treatment-related adverse events (TRAEs) were the secondary endpoints. Eligible patients were histopathologically and radiographically confirmed as having unresectable or mCRC, who had a performance status of 2 or less, adequate organ function, and had progressed from at least 2 lines of standard treatment, including fluoropyrimidines, irinotecan, oxaliplatin, with or without targeted drugs, such as BEV and cetuximab (only for *RAS* wild-type). Fruquintinib or regorafenib was permitted but not required for inclusion (*Figure 1*). This research was conducted in conformity with the Declaration of Helsinki (as revised in 2013). The Ethics Board of Hunan Cancer Hospital approved this study (No. 2023-39) and informed consent was provided by all individual participants.

Treatment

In the TAS-102 monotherapy group, TAS-102 35 mg/m² was administered orally twice a day on days 1–5 and 8–12, every 28 days, whereas in the TAS-102 plus BEV group, on days 1 and 15, every 28 days, patients received BEV (5 mg/kg, intravenously). BEV was delivered in a 30-minute intravenous infusion before TAS-102. For the first cycle, every patient received their initial conventional treatment

dose. For subsequent cycles, dose reductions of TAS-102 in 10 mg/d increments were implemented in patients with serious adverse events (AEs), particularly grade 3–4 neutropenia. A subsequent dose increase was not permitted in any patient, even when the AEs disappeared.

Assessment

Every 2 or 3 treatment cycles, the patients were assessed by computed tomography (CT) scans and clinical assessments until disease progression or loss to follow-up. According to the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1), at any time 1 measurable lesion was required. A total of 20 patients who received less than 2 cycles of TAS-102 could not be evaluated for PFS, ORR, or DCR, but we excluded those patients with missing follow-up data. ORR was regarded as the proportion of complete responses (CRs) and partial responses (PRs). DCR was defined as the addition of (CR + PR) rate and also stable disease (SD) rate. PFS was defined from the beginning of the therapy to the date of disease progression or death caused by any reason. OS was defined as the duration from the commencement of treatment to death. We evaluated toxicity according to the National Cancer Institute Common Terminology Criteria for Adverse Events 5.0 (NCI-CTCAE 5.0), and presented relevant results as numbers (%).

Statistical analysis

Continuous variables were evaluated by applying Student's *t*-test or Mann-Whitney *U* test, and expressed as the mean and standard deviation. Categorical data which were described as numbers (%) were assessed by χ^2 or Fisher exact test. PFS and OS in the TAS-102 monotherapy group and TAS-102 plus BEV group were inspected by Kaplan-Meier analysis. Under a Cox proportional-hazards model, hazard ratios (HRs) and associated 95% confidence intervals (CIs) were analyzed. The proportional-hazards assumption of OS was observed by graphical as well as analytical methods. Apart from that, alterations for varying confounding and risk factors were also included in this analysis. The results were described as point estimates and 95% CIs. All the statistical tests were 2-sided and a P value <0.05 was considered statistically significant. The analyses were performed with R software (version 3.6.0; R Foundation for Statistical Computing, Vienna, Austria). As this is a retrospective cohort study, sample size calculation was not performed. Eligible patients would be enrolled as many as possible.

Results

Patient characteristics

A total of 90 refractory mCRC patients were involved in this study. There were 32 patients in the TAS-102 monotherapy group and 58 patients in the TAS-102 plus BEV group (*Table 1*). Until the clinical cutoff date, January 13, 2023, for the efficacy and safety analyses, 58 (64.4%) of 90 patients remained alive during a median follow-up of 4.60 months (range, 0.20–22.80). All enrolled patients had received 5-fluorouracil (5-FU), oxaliplatin, and irinotecan. The median number of cycles was 1 (range, 1–17) for participants receiving TAS-102 and 2 (range, 1–26) for those who received TAS-102 plus BEV. There were no significant differences between the TAS-102 monotherapy group and the TAS-102 plus BEV group in baseline characteristics. The proportion of patients who previously received cetuximab, BEV, regorafenib, fruquintinib, and programmed cell death protein 1 (PD-1) was 34.4%, 84.4%, 25.0%, 34.4%, and 46.9% in the TAS-102 monotherapy group and 34.5%, 86.2%, 37.9%, 37.9%, and 48.3% in TAS-102 plus BEV group, respectively. A total of 18 (56.2%) of 32 patients and 35 (60.3%) of 58 patients had received 3 or more previous lines of therapy in the TAS-102 group. No marked difference occurred in the proportion of patients taking therapy after treatment between the TAS-102 group and the TAS-102 plus BEV group (21.9% *vs.* 31.0%, P=0.46).

Efficacy

A total of 32 (35.6%) of 90 patients died, 10 (31.2%) in the TAS-102 monotherapy group, and 22 (68.8%) in the TAS-102 plus BEV group. The mOS was 7.43 months (95% CI: 5.17–NA) in patients who received TAS-102 monotherapy and 10.83 months (95% CI: 10.10–NA) in patients who received TAS-102 plus BEV (P=0.78; *Figure 2*). PFS and ORR were evaluated in 70 patients, and no imaging evaluation was performed in the remaining 20 patients. Among the 70 patients, 45 (64.3%) of those progressed or even died. A total of 14 (31.1%) patients accepted TAS-102 and 31 (68.9%) patients accepted TAS-102 plus BEV. For patients who received TAS-102 monotherapy, the mPFS was 4.30 months (95% CI: 3.03–NA) and 4.67 months

Table 1 Baseline demographic and clinical characteristics (N=90)

Characteristics	Full sample (n=90)	TAS-102 (n=32)	TAS-102 + bevacizumab (n=58)	P value
Sex, n (%)				0.51
Men	45 (50.0)	18 (56.3)	27 (46.6)	
Women	45 (50.0)	14 (43.7)	31 (53.4)	
Age, year				0.62
Mean (SD)	55.2 (9.3)	55.9 (9.3)	54.8 (9.4)	
Median [min, max]	56 [33, 73]	57 [35, 71]	56 [33, 73]	
Age (years), n (%)				0.80
<60	67 (74.4)	23 (71.9)	44 (75.9)	
≥60	23 (25.6)	9 (28.1)	14 (24.1)	
Body mass index, kg/m^2				0.66
Mean (SD)	1.6 (0.2)	1.6 (0.2)	1.6 (0.2)	
Median [min, max]	1.6 [1.3, 2]	1.6 [1.3, 1.9]	1.6 [1.4, 2]	
ECOG PS, n (%)				0.36
0/1	89 (98.9)	31 (96.9)	58 (100.0)	
2	1 (1.1)	1 (3.1)	0	
Surgery, n (%)				0.33
No	12 (13.3)	6 (18.8)	6 (10.3)	
Yes	78 (86.7)	26 (81.2)	52 (89.7)	
Radiotherapy, n (%)				0.32
No	66 (73.3)	26 (81.3)	40 (69.0)	
Yes	24 (26.7)	6 (18.7)	18 (31.0)	
Primary tumor location, n (%)				0.15
Left colon	24 (26.7)	7 (21.9)	17 (29.3)	
Right colon	25 (27.8)	6 (18.7)	19 (32.8)	
Rectum	41 (45.5)	19 (59.4)	22 (37.9)	
Histological type of primary, n (%)				0.36
Adenocarcinoma	89 (98.9)	31 (96.9)	58 (100.0)	
Mucinous adenocarcinoma	1 (1.1)	1 (3.1)	0	
Liver metastases, n (%)				0.62
No	24 (26.7)	7 (21.9)	17 (29.3)	
Yes	66 (73.3)	25 (78.1)	41 (70.7)	
Lung metastases, n (%)				0.63
No	26 (28.9)	8 (25.0)	18 (31.0)	
Yes	64 (71.1)	24 (75.0)	40 (69.0)	

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	Full sample (n=90)	TAS-102 (n=32)	TAS-102 + bevacizumab (n=58)	P value
Lymph node metastases, n (%)				0.82
No	57 (63.3)	21 (65.6)	36 (62.1)	
Yes	33 (36.7)	11 (34.4)	22 (37.9)	
Bone metastases, n (%)				>0.99
No	75 (83.3)	27 (84.4)	48 (82.8)	
Yes	15 (16.7)	5 (15.6)	10 (17.2)	
Peritoneal metastases, n (%)				0.77
No	77 (85.6)	28 (87.5)	49 (84.5)	
Yes	13 (14.4)	4 (12.5)	9 (15.5)	
Adrenal metastases, n (%)				0.29
No	87 (96.7)	30 (93.8)	57 (98.3)	
Yes	3 (3.3)	2 (6.2)	1 (1.7)	
Ovarian metastases, n (%)				0.42
No	84 (93.3)	31 (96.9)	53 (91.4)	
Yes	6 (6.7)	1 (3.1)	5 (8.6)	
Pelvic metastases, n (%)				>0.99
No	76 (84.4)	27 (84.4)	49 (84.5)	
Yes	14 (15.6)	5 (15.6)	9 (15.5)	
Numbers of metastatic sites, n (%)				>0.99
One site	19 (21.1)	7 (21.9)	12 (20.7)	
≥ two sites	71 (78.9)	25 (78.1)	46 (79.3)	
MMR, n (%)				0.08
pMMR/MSS	74 (82.2)	23 (71.9)	51 (87.9)	
Unknown	16 (17.8)	9 (28.1)	7 (12.1)	
RAS, n (%)				0.83
RAS wild-type	33 (36.7)	10 (31.3)	23 (39.7)	
RAS mutant	42 (46.7)	16 (50.0)	26 (44.8)	
BRAF mutant	2 (2.2)	1 (3.1)	1 (1.7)	
Unknown	13 (14.4)	5 (15.6)	8 (13.8)	
Previous lines of chemotherapy, n (%)				0.82
Two lines	37 (41.1)	14 (43.8)	23 (39.7)	
≥ three lines	53 (58.9)	18 (56.2)	35 (60.3)	

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	Full sample (n=90)	TAS-102 (n=32)	TAS-102 + bevacizumab (n=58)	P value
Previous treatment agents				
Cetuximab, n (%)				>0.99
No	59 (65.6)	21 (65.6)	38 (65.5)	
Yes	31 (34.4)	11 (34.4)	20 (34.5)	
Bevacizumab, n (%)				>0.99
No	13 (14.4)	5 (15.6)	8 (13.8)	
Yes	77 (85.6)	27 (84.4)	50 (86.2)	
Regorafenib, n (%)				0.25
No	60 (66.7)	24 (75.0)	36 (62.1)	
Yes	30 (33.3)	8 (25.0)	22 (37.9)	
Fruquintinib, n (%)				0.82
No	57 (63.3)	21 (65.6)	36 (62.1)	
Yes	33 (36.7)	11 (34.4)	22 (37.9)	
PD-1, n (%)				>0.99
No	47 (52.2)	17 (53.1)	30 (51.7)	
Yes	43 (47.8)	15 (46.9)	28 (48.3)	
Lines of therapy after treatment, n (%)				0.46
No	65 (72.2)	25 (78.1)	40 (69.0)	
≥ one line	25 (27.8)	7 (21.9)	18 (31.0)	

TAS-102, trifluridine/tipiracil; SD, standard deviation; ECOG PS, Eastern Cooperative Oncology Group performance status; MMR, mismatch repair; pMMR, proficient MMR; MSS, microsatellite stability; PD-1, programmed cell death 1.

(95% CI: 3.57–7.37) in those receiving TAS-102 plus BEV (P=0.91; *Figure 3*). The DCR was reported in 13 (61.9%) patients in the TAS-102 monotherapy group and 38 (77.6%) patients in the TAS-102 plus BEV group (P=0.29). There were 6 (12.2%) patients in the TAS-102 plus BEV group who were confirmed to have a PR, but none had a CR. Thus, the ORR was 12.2%. No patients in the TAS-102 group had a PR or CR (P=0.31; *Table 2*).

Univariate and multivariate analysis

Among all 90 patients, univariate analysis showed that patients who had a performance status of 1 or less, previously undergone radiotherapy, and received therapy after treatment had extended OS (all P<0.05). There was no significant difference in OS between the TAS-102 group and the TAS-102 plus BEV group (P=0.78). In multivariate analysis, treatment strategy (with BEV or not) and important variables (all P<0.05) in the above univariate analysis were also included. Upon further multivariate analysis, we ascertained that undergoing therapy after treatment was a dependent predictor for OS (P<0.01) (*Table 3*).

Univariate analysis of 70 patients showed that those who had ovarian metastases, *RAS* wild-type, previously received cetuximab, had not received BEV before, and whose mismatch repair (MMR) status was unknown were considerably connected to PFS (all P<0.05). Meanwhile, multivariate analysis including all the above variables and the strategy (with BEV or not) confirmed that previous cetuximab treatment was an independent predictor for PFS (P=0.04) (*Table 4*).

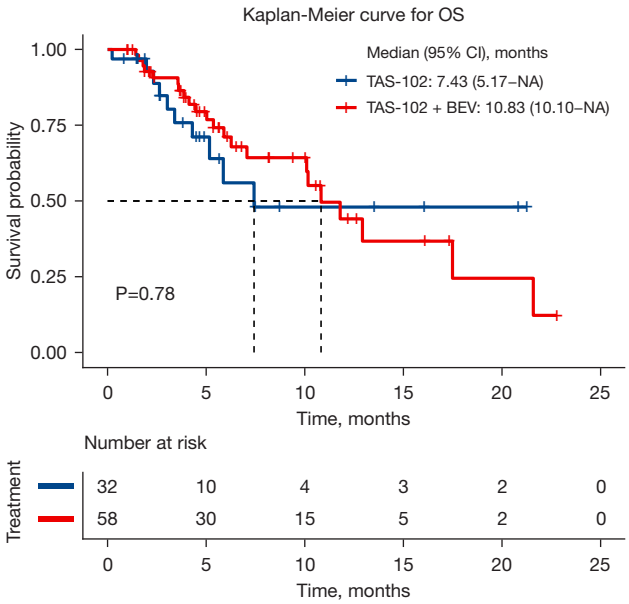

Figure 2 The Kaplan-Meier curves for the OS of patients in the TAS-102 group *vs.* patients in the TAS-102 + BEV group. OS, overall survival; TAS-102, trifluridine/tipiracil; BEV, bevacizumab; CI, confidence interval; NA, not available.

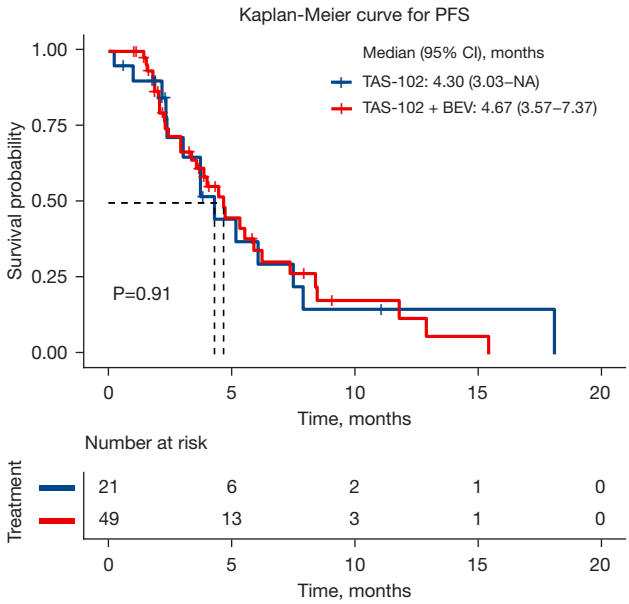

Figure 3 The Kaplan-Meier curves for the PFS of patients in the TAS-102 group *vs.* patients in the TAS-102 + BEV group. PFS, progression-free survival; TAS-102, trifluridine/tipiracil; BEV, bevacizumab; CI, confidence interval; NA, not available.

Table 2 Best tumor response of evaluable patients (RECIST 1.1)

Response	TAS-102 (N=21)	TAS-102 + bevacizumab (N=49)	P value
Complete response	0	0	
Partial response	0	6 (12.2)	0.16
Stable disease	13 (61.9)	32 (65.3)	>0.99
Progressive disease	8 (38.1)	11 (22.4)	0.50
Objective response rate	0	6 (12.2)	0.31
Disease control rate	13 (61.9)	38 (77.6)	0.29

TAS-102, trifluridine/tipiracil.

Safety

Safety assessments included all 90 treated patients. Any grade TRAEs were found in 25 (78.1%) patients in the TAS-102 group and 49 (84.5%) in the TAS-102 plus BEV (P=0.57). However, the incidence rate of serious adverse events (SAE) (≥ grade 3) basically remained the same between the 2 groups (34.4% *vs.* 29.3%, P=0.69). The SAEs in the TAS-102 monotherapy group included hemorrhage (n=1, caused by colon tumor rupture and bleeding), proteinuria (2 patients, 6.3%), vomiting (1 patient, 3.1%), leukopenia (3 patients, 9.4%), neutropenia (4 patients, 12.5%), decreased hemoglobin (1 patient, 3.1%), alanine aminotransferase (ALT) increase (1 patient, 3.1%), aspartate aminotransferase (AST) increase (3 patients, 9.4%) and total bilirubin (TBIL) increase (3 patients, 9.4%), and SAEs in the TAS-102 plus BEV group included leukopenia (8 patients, 13.8%), neutropenia (11 patients, 19.0%), decreased hemoglobin (9 patients, 15.5%), decreased platelet count (2 patients, 3.4%, which was much higher than in the TAS-102 monotherapy group, P=0.03), and TBIL increase (1 patient, 1.7%), respectively (*Table 5*).

Discussion

In our study, the mOS and mPFS of the TAS-102 monotherapy group were 7.43 months and 4.30 months, respectively. The results of mOS were generally consistent with the phase III trials RECOURSE and TERRA, but the results of mPFS was prolonged by more than 2 months (12,13). In our TAS-102 + BEV group, mOS was 10.8 months and mPFS was 4.6 months, which are consistent with the 9.4–11.2 and 4.29–5.6 months reported in previous studies, respectively (15-17). The SUNLIGHT trial is first the

Table 3 Univariate and multivariate Cox regression analysis of OS of 90 patients

Characteristics	No event (N=58)	Event (N=32)	UV		MV	
			HR (95% CI)	P value	HR (95% CI)	P value
Treatment				0.78		0.79
TAS-102	22 (37.9%)	10 (31.2%)	Reference		Reference	
TAS-102 + bevacizumab	36 (62.1%)	22 (68.8%)	0.90 (0.42, 1.92)		1.12 (0.48, 2.63)	
Sex				0.11		
Male	25 (43.1%)	20 (62.5%)	Reference			
Female	33 (56.9%)	12 (37.5%)	0.56 (0.27, 1.14)			
Age (years)				0.23		
<60	47 (81.0%)	20 (62.5%)	Reference			
≥60	11 (19.0%)	12 (37.5%)	1.55 (0.75, 3.20)			
ECOG PS				<0.01	Reference	0.10
0/1	58 (100.0%)	31 (96.9%)	Reference			
2	0	1 (3.1%)	10.8 (1.33, 88.2)		6.21 (0.69, 56.21)	
Surgery				0.59		
No	9 (15.5%)	3 (9.4%)	Reference			
Yes	49 (84.5%)	29 (90.6%)	1.39 (0.42, 4.58)			
Radiotherapy				0.02	Reference	0.11
No	40 (69.0%)	26 (81.2%)	Reference			
Yes	18 (31.0%)	6 (18.8%)	0.36 (0.15, 0.88)		0.45 (0.17, 1.20)	
Primary tumor location				0.15		
Left colon	14 (24.1%)	10 (31.2%)	Reference			
Right colon	14 (24.1%)	11 (34.4%)	0.69 (0.29, 1.65)			
Rectum	30 (51.7%)	11 (34.4%)	0.43 (0.18, 1.03)			
Liver metastases				0.17		
No	18 (31.0%)	6 (18.8%)	Reference			
Yes	40 (69.0%)	26 (81.2%)	1.86 (0.76, 4.53)			
Lung metastases				0.92		
No	17 (29.3%)	9 (28.1%)	Reference			
Yes	41 (70.7%)	23 (71.9%)	0.96 (0.44, 2.09)			
Lymph node metastases				0.11		
No	41 (70.7%)	16 (50.0%)	Reference			
Yes	17 (29.3%)	16 (50.0%)	1.77 (0.88, 3.59)			
Bone metastases				0.18		
No	52 (89.7%)	23 (71.9%)	Reference			
Yes	6 (10.3%)	9 (28.1%)	1.70 (0.77, 3.75)			

Table 3 (*continued*)

Table 3 (*continued*)

Characteristics	No event (N=58)	Event (N=32)	UV		MV	
			HR (95% CI)	P value	HR (95% CI)	P value
Peritoneal metastases				0.63		
No	48 (82.8%)	29 (90.6%)	Reference			
Yes	10 (17.2%)	3 (9.4%)	0.74 (0.22, 2.47)			
Adrenal metastases				0.58		
No	56 (96.6%)	31 (96.9%)	Reference			
Yes	2 (3.4%)	1 (3.1%)	1.74 (0.23, 13.1)			
Ovarian metastases				0.93		
No	54 (93.1%)	30 (93.8%)	Reference			
Yes	4 (6.9%)	2 (6.2%)	0.94 (0.22, 3.98)			
Pelvic metastases				0.09		
No	46 (79.3%)	30 (93.8%)	Reference			
Yes	12 (20.7%)	2 (6.2%)	0.30 (0.07, 1.28)			
Numbers of metastatic sites				0.50		
One site	13 (22.4%)	6 (18.8%)	Reference			
≥ two sites	45 (77.6%)	26 (81.2%)	1.36 (0.55, 3.35)			
MMR				0.18		
pMMR/MSS	46 (79.3%)	28 (87.5%)	Reference			
Unknown	12 (20.7%)	4 (12.5%)	0.49 (0.17, 1.43)			
RAS				0.19		0.25
RAS wild-type	26 (44.8%)	7 (21.9%)	Reference		Reference	
RAS mutant	24 (41.4%)	18 (56.2%)	2.51 (1.04, 6.07)		2.44 (0.93, 6.41)	
BRAF mutant	1 (1.7%)	1 (3.1%)	1.58 (0.19, 13.2)		3.67 (0.31, 43.31)	
Unknown	7 (12.1%)	6 (18.8%)	2.36 (0.78, 7.11)		1.62 (0.47, 5.56)	
Previous lines of chemotherapy				0.33		
Two lines	24 (41.4%)	13 (40.6%)	Reference			
≥ three lines	34 (58.6%)	19 (59.4%)	0.70 (0.34, 1.44)			
Previous treatment agents						
Cetuximab				0.17		
No	35 (60.3%)	24 (75.0%)	Reference			
Yes	23 (39.7%)	8 (25.0%)	0.58 (0.26, 1.29)			
Bevacizumab				0.10		0.23
No	10 (17.2%)	3 (9.4%)	Reference		Reference	
Yes	48 (82.8%)	29 (90.6%)	2.70 (0.81, 9.07)		2.44 (0.56, 10.56)	

Table 3 (*continued*)

Table 3 (*continued*)

Characteristics	No event (N=58)	Event (N=32)	UV		MV	
			HR (95% CI)	P value	HR (95% CI)	P value
Regorafenib				0.94		
No	43 (74.1%)	17 (53.1%)	Reference			
Yes	15 (25.9%)	15 (46.9%)	1.03 (0.50, 2.14)			
Fruquintinib				0.90		
No	36 (62.1%)	21 (65.6%)	Reference			
Yes	22 (37.9%)	11 (34.4%)	1.05 (0.50, 2.20)			
PD-1				0.61		
No	31 (53.4%)	16 (50.0%)	Reference			
Yes	27 (46.6%)	16 (50.0%)	0.83 (0.41, 1.68)			
Lines of therapy after treatment				<0.01		<0.01
No	40 (69.0%)	25 (78.1%)	Reference		Reference	
≥ one line	18 (31.0%)	7 (21.9%)	0.22 (0.08, 0.59)		0.25 (0.09, 0.71)	

OS, overall survival; UV, univariate analysis; MV, multivariate analysis; HR, hazard ratio; CI, confidence interval; TAS-102, trifluridine/tipiracil; ECOG PS, Eastern Cooperative Oncology Group performance status; MMR, mismatch repair; pMMR, proficient MMR; MSS, microsatellite stability; PD-1, programmed cell death protein 1.

Table 4 Univariate and multivariate Cox regression analysis of PFS of 70 patients

Characteristics	No event (N=25)	Event (N=45)	UV		MV	
			HR (95% CI)	P value	HR (95% CI)	P value
Treatment				0.91		0.96
TAS-102	7 (28.0%)	14 (31.1%)	Reference			
TAS-102 + bevacizumab	18 (72.0%)	31 (68.9%)	1.04 (0.54, 1.99)		0.98 (0.46, 2.07)	
Sex				0.55		
Male	14 (56.0%)	22 (48.9%)	Reference			
Female	11 (44.0%)	23 (51.1%)	1.20 (0.66, 2.18)			
Age (years)				0.42		
<60	19 (76.0%)	32 (71.1%)	Reference			
≥60	6 (24.0%)	13 (28.9%)	0.76 (0.40, 1.47)			
ECOG PS				0.16		
0/1	25 (100.0%)	44 (97.8%)	Reference			
2	0	1 (2.2%)	3.81 (0.50, 29.0)			
Surgery				0.38		
No	3 (12.0%)	4 (8.9%)	Reference			
Yes	22 (88.0%)	41 (91.1%)	1.70 (0.51, 5.65)			

Table 4 (*continued*)

Table 4 (*continued*)

Characteristics	No event (N=25)	Event (N=45)	UV		MV	
			HR (95% CI)	P value	HR (95% CI)	P value
Radiotherapy				0.41		0.42
No	17 (68.0%)	31 (68.9%)	Reference		Reference	
Yes	8 (32.0%)	14 (31.1%)	0.76 (0.40, 1.45)		0.74 (0.35, 1.54)	
Primary tumor location				0.60		
Left colon	5 (20.0%)	9 (20.0%)	Reference			
Right colon	9 (36.0%)	13 (28.9%)	1.16 (0.49, 2.77)			
Rectum	11 (44.0%)	23 (51.1%)	0.82 (0.37, 1.79)			
Liver metastases				0.38		
No	9 (36.0%)	10 (22.2%)	Reference			
Yes	16 (64.0%)	35 (77.8%)	1.37 (0.67, 2.78)			
Lung metastases				0.58		
No	6 (24.0%)	12 (26.7%)	Reference			
Yes	19 (76.0%)	33 (73.3%)	0.83 (0.42, 1.62)			
Lymph node metastases				0.94		
No	15 (60.0%)	29 (64.4%)	Reference			
Yes	10 (40.0%)	16 (35.6%)	0.97 (0.52, 1.84)			
Bone metastases				0.47		
No	22 (88.0%)	36 (80.0%)	Reference			
Yes	3 (12.0%)	9 (20.0%)	1.31 (0.62, 2.76)			
Peritoneal metastases				0.14		
No	22 (88.0%)	38 (84.4%)	Reference			
Yes	3 (12.0%)	7 (15.6%)	1.86 (0.81, 4.27)			
Adrenal metastases				0.34		
No	24 (96.0%)	44 (97.8%)	Reference			
Yes	1 (4.0%)	1 (2.2%)	2.59 (0.34, 19.5)			
Ovarian metastases				0.03		0.69
No	24 (96.0%)	41 (91.1%)	Reference		Reference	
Yes	1 (4.0%)	4 (8.9%)	2.99 (1.05, 8.54)		1.27 (0.39, 4.17)	
Pelvic metastases				0.77		
No	22 (88.0%)	39 (86.7%)	Reference			
Yes	3 (12.0%)	6 (13.3%)	0.88 (0.37, 2.09)			

Table 4 (*continued*)

Table 4 (*continued*)

Characteristics	No event (N=25)	Event (N=45)	UV		MV	
			HR (95% CI)	P value	HR (95% CI)	P value
Numbers of metastatic sites				0.62		
One site	6 (24.0%)	10 (22.2%)	Reference			
≥ two sites	19 (76.0%)	35 (77.8%)	1.20 (0.59, 2.43)			
MMR				0.03		0.054
pMMR/MSS	20 (80.0%)	39 (86.7%)	Reference		Reference	
Unknown	5 (20.0%)	6 (13.3%)	0.37 (0.14, 0.96)		0.25 (0.06, 1.03)	
RAS				<0.01		0.10
RAS wild-type	13 (52.0%)	13 (28.9%)	Reference		Reference	
RAS mutant	8 (32.0%)	26 (57.8%)	3.71 (1.71, 8.05)		0.73 (0.16, 3.4)	
BRAF mutant	1 (4.0%)	1 (2.2%)	0.39 (0.05, 3.23)		0.03 (1.4e–03, 0.68)	
Unknown	3 (12.0%)	5 (11.1%)	1.15 (0.40, 3.30)		0.47 (0.08, 2.81)	
Previous lines of chemotherapy				0.89		
Two lines	12 (48.0%)	14 (31.1%)	Reference			
≥ three lines	13 (52.0%)	31 (68.9%)	0.95 (0.50, 1.83)			
Previous treatment agents						
Cetuximab				<0.01		0.04
No	12 (48.0%)	34 (75.6%)	Reference		Reference	
Yes	13 (52.0%)	11 (24.4%)	0.40 (0.19, 0.81)		0.17 (0.03, 0.91)	
Bevacizumab				0.03		0.84
No	5 (20.0%)	6 (13.3%)	Reference		Reference	
Yes	20 (80.0%)	39 (86.7%)	3.03 (1.06, 8.69)		0.88 (0.24, 3.18)	
Regorafenib				0.31		
No	19 (76.0%)	24 (53.3%)	Reference			
Yes	6 (24.0%)	21 (46.7%)	0.72 (0.38, 1.36)			
Fruquintinib				0.23		
No	18 (72.0%)	26 (57.8%)	Reference			
Yes	7 (28.0%)	19 (42.2%)	1.44 (0.79, 2.64)			
PD-1				0.19		
No	13 (52.0%)	21 (46.7%)	Reference			
Yes	12 (48.0%)	24 (53.3%)	0.67 (0.37, 1.22)			
Lines of therapy after treatment				0.56		
No	21 (84.0%)	24 (53.3%)	Reference			
≥ one line	4 (16.0%)	21 (46.7%)	0.83 (0.45, 1.56)			

TAS-102, trifluridine/tipiracil; ECOG PS, Eastern Cooperative Oncology Group performance status; MMR, mismatch repair; MSS, microsatellite stability; HR, hazard ratio; PD-1, programmed cell death protein 1; UV, univariate analysis; MV, multivariate analysis.

Table 5 Treatment-related adverse events

Adverse events	Full sample (n=90)	TAS-102 (n=32)	TAS-102 + bevacizumab (n=58)	P value
Hypertension				0.42
Grade 0	71 (78.9)	28 (87.5)	43 (74.1)	
Grade 1	11 (12.2)	2 (6.3)	9 (15.5)	
Grade 2	8 (8.9)	2 (6.3)	6 (10.3)	
Hemorrhage				0.36
Grade 0	89 (98.9)	31 (96.9)	58 (100.0)	
Grade 3	1 (1.1)	1 (3.1)	0	
Proteinuria				0.18
Grade 0	80 (88.9)	29 (90.6)	51 (87.9)	
Grade 1	6 (6.7)	1 (3.1)	5 (8.6)	
Grade 2	2 (2.2)	0	2 (3.4)	
Grade ≥3	2 (2.2)	2 (6.3)	0	
Fatigue				0.35
Grade 0	62 (68.9)	20 (62.5)	42 (72.4)	
Grade 1	28 (31.1)	12 (37.5)	16 (27.6)	
Anorexia				0.08
Grade 0	49 (54.4)	13 (40.6)	36 (62.1)	
Grade 1	41 (45.6)	19 (59.4)	22 (37.9)	
Nausea				0.07
Grade 0	66 (73.3)	20 (62.5)	46 (79.3)	
Grade 1	22 (24.4)	10 (31.3)	12 (20.7)	
Grade 2	2 (2.2)	2 (6.3)	0	
Vomiting				0.23
Grade 0	86 (95.6)	29 (90.6)	57 (98.3)	
Grade 1	2 (2.2)	1 (3.1)	1 (1.7)	
Grade 2	1 (1.1)	1 (3.1)	0	
Grade ≥3	1 (1.1)	1 (3.1)	0	
Leukopenia				0.67
Grade 0	46 (51.1)	19 (59.4)	27 (46.6)	
Grade 1	17 (18.9)	6 (18.8)	11 (19.0)	
Grade 2	16 (17.8)	4 (12.5)	12 (20.7)	
Grade ≥3	11 (12.2)	3 (9.4)	8 (13.8)	
Neutropenia				0.29
Grade 0	50 (55.6)	22 (68.8)	28 (48.3)	
Grade 1	12 (13.3)	2 (6.3)	10 (17.2)	
Grade 2	13 (14.4)	4 (12.5)	9 (15.5)	
Grade ≥3	15 (16.7)	4 (12.5)	11 (19.0)	

Table 5 (*continued*)

Table 5 (*continued*)

Adverse events	Full sample (n=90)	TAS-102 (n=32)	TAS-102 + bevacizumab (n=58)	P value
Hemoglobin decreased				0.25
Grade 0	48 (53.3)	17 (53.1)	31 (53.4)	
Grade 1	20 (22.2)	8 (25.0)	12 (20.7)	
Grade 2	12 (13.3)	6 (18.8)	6 (10.3)	
Grade ≥3	10 (11.1)	1 (3.1)	9 (15.5)	
Platelet count decrease				0.03
Grade 0	80 (88.9)	31 (96.9)	49 (84.5)	
Grade 1	7 (7.8)	0	7 (12.1)	
Grade 2	1 (1.1)	1 (3.1)	0	
Grade ≥3	2 (2.2)	0	2 (3.4)	
ALT increase				0.43
Grade 0	72 (80.0)	26 (81.3)	46 (79.3)	
Grade 1	10 (11.1)	2 (6.3)	8 (13.8)	
Grade 2	7 (7.8)	3 (9.4)	4 (6.9)	
Grade ≥3	1 (1.1)	1 (3.1)	0	
AST increase				0.09
Grade 0	63 (70.0)	22 (68.8)	41 (70.7)	
Grade 1	21 (23.3)	7 (21.9)	14 (24.1)	
Grade 2	3 (3.3)	0	3 (5.2)	
Grade ≥3	3 (3.3)	3 (9.4)	0	
TBIL increase				0.14
Grade 0	66 (73.3)	24 (75.0)	42 (72.4)	
Grade 1	13 (14.4)	2 (6.3)	11 (19.0)	
Grade 2	7 (7.8)	3 (9.4)	4 (6.9)	
Grade ≥3	4 (4.4)	3 (9.4)	1 (1.7)	
Adverse				0.57
Grade 0	16 (17.8)	7 (21.9)	9 (15.5)	
Any grade	74 (82.2)	25 (78.1)	49 (84.5)	
Adverse				0.69
Grade 0	16 (17.8)	7 (21.9)	9 (15.5)	
Grade 1	20 (22.2)	7 (21.9)	13 (22.4)	
Grade 2	26 (28.9)	7 (21.9)	19 (32.8)	
Grade ≥3	28 (31.1)	11 (34.4)	17 (29.3)	

Data are presented as n (%). TAS-102, trifluridine/tipiracil; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin.

unique phase III randomized controlled trial to confirm that TAS-102 combined with BEV can prolong survival in patients with refractory mCRC (19). The TAS-102 plus BEV group in the SUNLIGHT trial showed a mOS of 10.8 months, which is consistent with our result. Moreover, our ORR not only significantly exceeded that reported in the C-TASK FORCE and BiTS studies (both 0% by central assessment), and another Danish study (2%) (15-17), but was also higher than the results of the SUNLINGT study (6.3%).

In addition, PFS and OS were improved with TAS-102 plus BEV, compared with TAS-102 monotherapy, but there was no statistically significant difference. The reasons are as follows: First, although TAS-102 monotherapy has been recommended by several guidelines as a therapeutic agent for refractory mCRC, previous small sample studies have shown that BEV combined with TAS-102 can prolong PFS and OS (12,13). In our hospital, physicians have preferred to administer TAS-102 combined with BEV, resulting in only 32 patients receiving TAS-102 monotherapy from November 2020 to October 2022. The sample size in the TAS-102 monotherapy group was too small. Second, in the TAS-102 + BEV group, the ratio of patients with right-sided colon cancer was comparatively high, (33% *vs.* 19%) who had worse prognosis and shorter survival (20), resulting a shorter OS. Third, in the TAS-102 monotherapy group, 1 patient with liver metastases had undergone radiofrequency ablation (RFA) of liver metastases, whose PFS had not been reached at the data cutoff on January 13, 2023. This has possibly resulted in very similar mPFS between the 2 groups (4.30 months in TAS-102 monotherapy group *vs.* 4.67 months in the TAS-102 plus BEV group). Finally, although the mOS was improved from 7.43 months to 10.83 months in patients who received TAS-102 + BEV compared with those who underwent TAS-102 monotherapy, there was an almost imperceptible difference between them (P=0.78). However, at the data cutoff on January 13, 2023, 58 (64.4%) of 90 patients were alive, and the results may change with longer follow-up.

We will continue to use the pathological tissue specimens and blood samples collected in our study to find predictive and prognostic markers. TAS-102 plus BEV is an encouraging regimen for refractory mCRC. Several clinical trials have already been conducted to investigate the benefit of this combination therapy in the beginning of treatment for patients with mCRC, especially older patients who are not suitable for intensive chemotherapy. The phase II TASCO1 study evaluated the efficacy and safety of TAS-102 plus BEV compared with capecitabine plus BEV as first-line therapy in patients who were unsuitable for intensive chemotherapy, which showed that TAS-102 combined with BEV had promising clinical activity and a tolerable safety profile (21). Furthermore, in the KSCC1602 study, the combination was effective in the first-line treatment of elderly patients (ORR 40.5%, DCR 86.5%) (22). A large, randomized, controlled phase III trial, SOLSTICE, indicates that TAS-102 plus BEV represents a feasible alternative in patients with mCRC ineligible for intensive treatment (23). We are confident that the longer survival, higher ORR, and tolerable additional toxicity that have been observed provide support for the use of TAS-102 plus BEV in patients with refractory mCRC.

Despite some encouraging results from our study, there are still some limitations First, the study was conducted in a single center and retrospectively. Thus, the AEs for patients who were not in the hospital could not be fully recorded, leading to possible underestimation of AE incidence. Second, 20 (22.2%) patients in our study did not return for evaluation or further treatment due to financial, medical insurance, COVID-19, TRAEs, or other unknown reasons, which may have influenced the primary end point of OS, especially the secondary end points of PFS and ORR. Third, in China's medical insurance, TAS-102 is self-paid and cannot be reimbursed. The high medical cost leads to few patients using it for a prolonged period. Since TAS-102 was approved in China on August 29, 2019, only 90 cases met the eligibility criteria of our study in our center. Sample size limitations can also affect the results. However, our study is the largest ever published. Lastly, the sample size of this study was small and consideration of confounding factors may not be sufficient. We highly expect the publication of the original article of the phase III randomized controlled study SUNLIGHT to elucidate the final results and details, and guide us to further explore the optimal population to benefit from TAS-102 combined with BEV.

Conclusions

In conclusion, this retrospective cohort study demonstrated that TAS-102 combined with BEV during the treatment of Chinese patients with refractory mCRC trended to improve ORR and survival and had a safe profile, findings which are consistent with previous studies and even the SUNLIGHT study. Thus, TAS-102 plus BEV is worthy of a prospective

study comparing with TAS-102 monotherapy Chinese patients with refractory mCRC.

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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-24-98/rc

Data Sharing Statement: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-98/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-98/coif). The authors have no conflicts of interest to declare.

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 (as revised in 2013). The study was approved by the Ethics Board of Hunan Cancer Hospital (No. 2023-39) and informed consent was provided by all individual participants.

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