Efficacy, safety, and predictors of fruquintinib plus anti-programmed death receptor-1 (PD-1) antibody in refractory microsatellite stable metastatic colorectal cancer in a real-world setting: a retrospective cohort study

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Background: Patients with microsatellite stable (MSS) advanced colorectal cancer (CRC) have few alternatives for salvage therapy and a large unmet clinical need. Preclinical studies demonstrate that fruquintinib combined with anti-programmed death protein 1 (PD-1) has a synergistic anti-tumor effect. But a few phase 2 clinical studies show inconsistent efficacy of this combination therapy in CRC. The aim of this study was to investigate the efficacy, safety, and predictors of fruquintinib plus PD-1 antibodies in refractory MSS metastatic CRC (mCRC) in a real-world setting.

Methods: We performed a retrospective single-center analysis to assess the outcomes of patients with MSS mCRC who were treated with fruquintinib plus anti-PD-1 antibodies subsequent to the failure of standard therapies at the Hunan Cancer Hospital. The overall survival (OS), progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR), and toxicity were reviewed and evaluated. The primary endpoint was OS. The impact on OS and PFS was examined using the Cox regression model.

Results: Between 1 January 2019 and 30 June 2022, we enrolled 70 eligible patients. The median follow-up was 17.2 months (range, 5.3–32.9 months). The median OS (mOS) and median PFS (mPFS) were 19.48 and 5.5 months respectively. The ORR was 11.43% and the DCR was 84.29%. Multivariate Cox regression analysis reveals liver metastasis (LM) without local treatment was a risk factor for OS [hazard ratio (HR) =5.31, P=0.0184], whereas that with local treatment (HR =2.19, P=0.263) was not. The most common adverse events were hand-foot syndrome (37.14%), hypertension (34.29%), mucositis oral (32.86%). No serious adverse effects or adverse effect-related deaths were reported. There were no instances of severe adverse effects or deaths related to adverse effects reported.

Conclusions: Our study indicates that the combination of fruquintinib and anti-PD-1 antibodies can improve the OS and PFS with a tolerable toxicity profile for Chinese patients with refractory MSS mCRC. LM without local therapy is a negative prognostic factor for OS, but those with local treatment can significantly prolong survival. We require additional well-structured, prospective, and extensive studies to

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confirm and validate these findings.

Introduction

Globally, colorectal cancer (CRC) is the primary cause of cancer-related mortality (1). The survival rate of refractory CRC is dismal and therapeutic options are limited after the standard chemotherapy with or without targeted drugs. Currently, regorafenib and trifluridine/tipiracil (TAS-102) are recommended as the third-line treatment regimen for metastatic CRC (mCRC) patients (2,3). Fruquintinib is a highly selective small-molecule inhibitor of VEGFR1, VEGFR2, and VEGFR3 that is administered orally and exhibits potent activity. In light of the FRESCO study's findings (4), the National Medical Products Administration (NMPA) has granted regulatory approval for the use of fruquintinib in the third-line treatment of advanced CRC. Both regorafenib and fruquintinib are antiangiogenic medications used as third-line therapies for advanced CRC.

Highlight box

Key findings
- We observed the median overall survival and median progression-free survival were 19.48 and 5.5 months respectively in a real world study.
- Liver metastases is poor prognostic factor, however addition of local treatment can significantly prolong patient survival.

What is known and what is new?
- The survival rate of refractory colorectal cancer (CRC) is dismal. Anti-programmed death protein 1 (PD-1) antibody nearly no activity in microsatellite stable (MSS) metastatic CRC (mCRC). Anti-angiogenesis combined with anti-PD-1 therapies has synergistic anti-tumor activity.
- This study evaluated and analyzed the clinical effect of fruquintinib plus anti-PD-1 antibody in refractory MSS mCRC.

What is the implication, and what should change now?
- In refractory MSS mCRC patients, the combination of fruquintinib and anti-PD-1 antibody is a promising treatment option, significantly improve prognosis, but further prospective studies need to be conducted.

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but the progression-free survival (PFS) and overall survival (OS) of monotherapy are around 3–4 and 7–9 months, respectively, and the objective response rate (ORR) is <5%. Thus, the development of more effective treatments for patients with this disease is an urgent unmet need. Current exploration directions for salvage therapy in advanced refractory CRC include the combining anti-VEGF/VEGFR agents with either chemotherapy (5-8) or PD-1 inhibitors. Anti-programmed death protein 1 (PD-1) antibody has demonstrated the amazing anti-oncogenesis activity in microsatellite instability-high (MSI-H) mCRC (9), but the ORR is 0% in the microsatellite stable (MSS) mCRC (10). Approximately 95% of mCRC patients are MSS and given that the inhibition of the PD-1/programmed death ligand 1 (PD-L1) axis alone has proven insufficient for proficient mismatch repair (pMMR)/MSS mCRC, to overcome immune resistance in this condition, the combination of an antiangiogenic agent with immunotherapy have been explored. Vascular abnormality is a hallmark of most solid tumors and facilitates immune evasion. Tumor angiogenesis not only facilitates tumor growth and metastasis but also constructs an immunosuppressive tumor microenvironment (TME), rendering it resistant to immunotherapy.

Growing data in recent years has demonstrated that anti-angiogenesis therapy can initiate anti-tumor CD8^{+} T cell immunity and infiltrate, possibly through endothelial cell activation and vascular normalization (11,12), and Treg cell infiltration is continuously inhibited. Therefore, the inherently immunosuppressive tumor microenvironment shifts towards an immune-supportive state, subsequently amplifying the efficacy of anti-PD-1 therapies (13). However, the efficacy of the combination of small molecule anti-angiogenic drugs and PD-1 inhibitors is controversial, and the conclusions are not consistent.

The combination of nivolumab and regorafenib demonstrates promising antitumor effects in a CRC group participating in the phase Ib REGONIVO study. Among 24 Japanese patients with MSS mCRC, the ORR was 33%,

with a median PFS of 7.9 months, while the median OS had not yet been reached (14). Subsequent similar study has yielded highly conflicting results. The North American REGONIVO study demonstrated an overall ORR of 7%, with no response observed (0%) specifically in patients presenting with concomitant liver metastases (15). Another similar study, REGOMUNE, which employed regorafenib in combination with avelumab, also failed to achieve comparable efficacy (16), the ORR was 0%, the median PFS and OS were 3.6 and 10.8 months, respectively. The reasons for this difference in these findings are unclear and may be related to differences in PD-1 drugs, variations in regorafenib dosages, ethnic differences, and biases resulting from small sample sizes. There is currently no ongoing phase 3 clinical trial investigating the combined use of fruquintinib with PD-1 inhibitors. The existing phase 1b/2 prospective studies, limited by small sample sizes and insufficient follow-up time, individually demonstrate ORRs of 21.5%, 26%, and 20%, respectively, surpassing the efficacy seen with fruquintinib monotherapy (17-19). However, due to the limited sample size, further exploration is warranted to assess the effectiveness of fruquintinib in conjunction with PD-1 inhibitors and to identify potential beneficiary subgroups. Here, with a larger sample size and longer follow-up length, we sought to examine the safety, risks, and effectiveness of fruquintinib + anti-PD-1 antibodies in refractory MSS mCRC in a real-world context. This study aims to provide a more realistic insight into the treatment's actual effectiveness and safety within authentic clinical settings with reduced costs. We present this article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-931/rc).

Methods

This retrospective study was approved by the independent ethics committee of the Hunan Cancer Hospital (No. 2023-55) and conducted in accordance with the Helsinki Declaration (as revised in 2013) and the requirement of informed consent was waived by the Ethics Committee due to the observational retrospective design. The study was registered with ClinicalTrials.gov (number, NCT 06011330).

Study design and participants

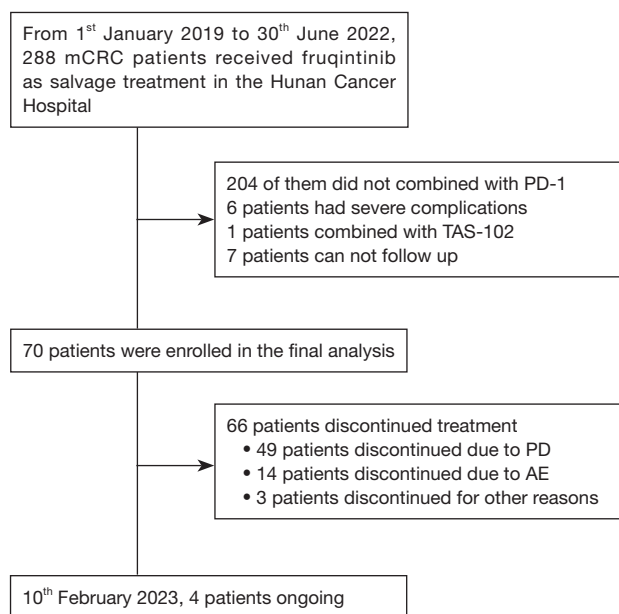Retrospective single-arm, single-center studies were conducted on MSS/pMMR mCRC patients who received fruquintinib and anti-PD-1 antibodies as third-line or subsequent therapies at Hunan Cancer Hospital between January 1, 2019, and June 30, 2022. The inclusion criteria were: (I) aged 18 years or older; (II) with histologically or cytologically confirmed adenocarcinoma of the colon or rectum; (III) following disease progression after a minimum of two lines of standard chemotherapy, incorporating fluorouracil, oxaliplatin, and irinotecan, either in combination with or without targeted medications like cetuximab and bevacizumab; (IV) patients had at least 1 non-resectable measurable lesion to evaluate according to the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1); (V) MMR proteins or MSI testing was accomplished by immunohistochemistry (IHC) or polymerase chain reaction (PCR). Other eligibility criteria included an Eastern Cooperative Oncology Group performance status of 0–2, prior treatment with TAS-102, regorafenib, and anti-PD-1 antibody was allowed. The exclusion criteria comprised: (I) patients who received fewer than one treatment cycle; (II) patients experiencing multiple complications; (III) patients with dMMR or MSI-H; (IV) concurrent administration of other chemotherapy drugs.

Treatment

The PD-1 inhibitor was intravenously administered on day 1, with recommended dosages as follows: nivolumab at 240 mg every 2 weeks; pembrolizumab, tislelizumab, and sintilimab at 200 mg every 3 weeks; and toripalimab at 240 mg every 3 weeks. Fruquintinib was orally administered once daily in a 28-day cycle (21 day on /7 day off). The treatment initiated at 5 mg, with potential adjustments to 3 or 4 mg later in the cycle if the initial dosage isn't well tolerated.

Assessments

Patients were followed up until the cutoff date of 10 February 2023 or being lost to follow-up. All of the patients were followed up at 2-monthly periods after the initiation of treatment. Patients who failed to attend their follow-up visit were sent an e-mail or letter and received a phone call. The primary endpoint was set as OS. OS was measured as the time from the study-specific treatment to death for any reason. Data on patient deaths were obtained from the government's death registry. The second endpoint, PFS, was defined as the duration from the start of treatment to

From 1st January 2019 to 30th June 2022, 288 mCRC patients received fruqintinib as salvage treatment in the Hunan Cancer Hospital

204 of them did not combined with PD-1
6 patients had severe complications
1 patients combined with TAS-102
7 patients can not follow up

70 patients were enrolled in the final analysis

66 patients discontinued treatment
• 49 patients discontinued due to PD
• 14 patients discontinued due to AE
• 3 patients discontinued for other reasons

10th February 2023, 4 patients ongoing

Figure 1 Flowchart of the whole study. mCRC, metastatic colorectal cancer; PD-1, programmed cell death protein 1; PD, progressive disease; AE, adverse events. TAS-102, trifluridine/tipiracil.

the RECIST-defined progression of the disease or death, whichever occurs first.

Tumor measurements were conducted using computed tomography (CT) scans every 8 weeks, following RECIST version 1.1 guidelines, until disease progression or the initiation of subsequent treatment. Assessment of tumor response encompassed complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). Additionally, evaluations included the calculation of the ORR as the combined sum of CR and PR, while the disease control rate (DCR) was calculated as the combined sum of CR, PR, and SD.

Adverse events, laboratory abnormalities (hematology, clinical chemistry, and urinalysis), vital signs, electrocardiograms, and echocardiograms were all considered in the safety evaluations. The Common Terminology Criteria for Adverse Events, version 4.03 of the National Cancer Institute, was used to grade treatment-related adverse events (TRAEs) (20).

Statistical analysis

Statistical sample size calculation: enrollment duration of 18 months, follow-up period of 18 months, two-tailed α=0.05, power =0.8, primary endpoint is OS. In comparison

to the FRESCO study which had a median OS of 9.3 months, aiming to elevate it to 15 months, the sample size was estimated at 49 cases, considering a dropout rate of 20%. The anticipated final sample size was 62 cases. However, 70 cases were actually enrolled. Efficacy and safety were analyzed in all patients who received at least 1 cycle of treatment. The baseline characteristics were described with n (%) or median [95% confidence interval (CI)] appropriately. OS and PFS were estimated using the Kaplan-Meier method, while the log-rank test determined survival curve disparities. Variables with $P<0.05$ in univariate analysis were assessed using the Cox regression model. Calculations included the hazard ratio (HR) and 95% CI to analyze their impact. Statistical significance was established at $P<0.05$. All data were analyzed using R 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics

We enrolled 70 eligible patients with MSS/pMMR mCRC. *Figure 1* illustrates the flow chart for the patient selection process. Clinical characteristics of the patients are listed in *Table 1*. The median age was 59 (range, 35–76) years, and 37 (52.86%) were male. Out of the total, 47 patients (67.14%) had undergone treatment beyond the third line. Liver metastasis (LM) was present in 51 patients (72.86%) and 24 (47.06%) of those with LM received local treatment [ablation, stereotactic body radiation therapy (SBRT), or surgery]. Of the patients, 53 (75.71%) had lung metastases. A total of 28 (40%) patients had already received regorafenib for advanced disease, and 17 (24.3%) patients had already received anti-PD-1 antibody. Some 75.7% of the patients used sintilimab, and 18.6% of the patients used toripalimab. The median number of cycles of fruquintinib plus anti-PD-1 antibodies administration was 4 (range, 1–18). A total of 61 patients used more than or equal to 2 cycles.
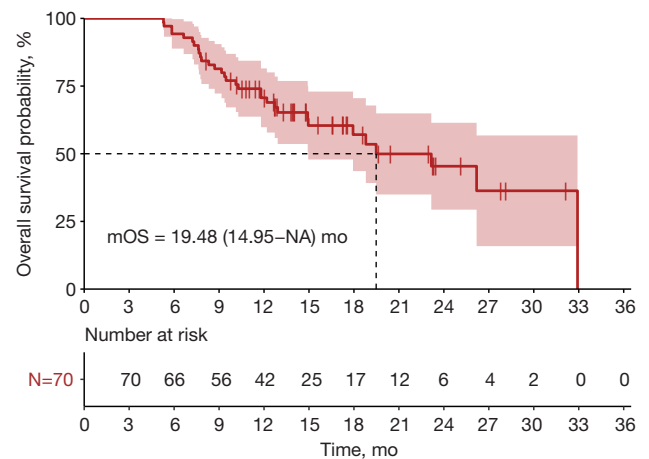
Clinical efficacy

The cut-off date was 10 February 2023. The median follow-up was 17.2 months (range, 5.3–32.9 months). A total of 39 (55.7%) patients were still alive, among whom 4 patients were still receiving study treatment up to the cut-off date. Treatment discontinuation primarily resulted from PD (n=49, 70.00%). The mOS and mPFS were 19.48 months

Table 1 Baseline characteristics

Characteristics	Number (n=70)
Male	37 (52.86)
Age, year	
Median [range]	59 [35–76]
≥65	11 (15.71)
ECOG PS of 1[a]	67 (95.71)
Normal BMI (kg/m^2)	64 (91.43)
Left-located primary tumor	44 (62.86)
Metastases	
Lung	53 (75.71)
Liver	51 (72.86)
Peritoneum	16 (22.86)
Lymph node	27 (38.57)
Omentum	7 (10.00)
Bone	12 (17.14)
Metastases ≥3	44 (62.86)
Failed second-line therapy	24 (34.29)
Surgery	52 (74.29)
KRAS mutation	
Wild	29 (41.43)
Mutant	37 (52.86)
Unknown	4 (5.71)
Local treatment for liver metastasis	
Yes	24 (34.29)
No	27 (38.57)
Prior regorafenib	28 (40.00)

Data are reported as No. (%) unless otherwise indicated. [a], all patients were of ECOG PS 1 or 2. ECOG PS, Eastern Cooperative Oncology Group performance status; BMI, body mass index.

Figure 2 The KM-plot of overall survival. mOS, median overall survival; NA, not applicable; mo, month; KM, Kaplan-Meier.
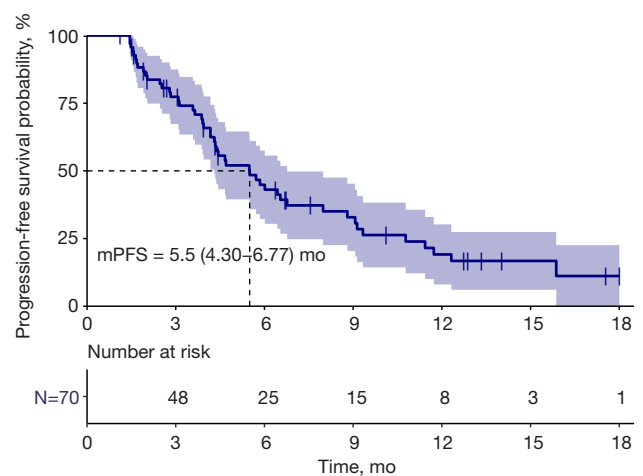
**Figure 3** The KM-plot of progression-free survival. mPFS, median progression-free survival; mo, month; KM, Kaplan-Meier.

[95% CI: 14.95–not available (NA)] and 5.5 months (95% CI: 4.30–6.77), respectively (*Figures 2,3*). There was no significant difference in mOS between patients with LM or non-liver metastases (NLM) (18.76 months *vs.* NA, P=0.19; *Figure 4A*). However, at the 1-year landmark analysis, NLM (n=11) had better mOS than LM (n=31, P=0.046; *Figure 4B*). Moreover, patients with LM who underwent local treatment had a significantly better mOS than those who did not receive local treatment (23.13 *vs.* 12.16 months,

P=0.034; *Figure 5*). Additionally, the mOS of patients with LM who underwent local treatment was not significantly different to those with NLM (23.13 *vs.* NA, P=0.69).

None of the patients achieved CR. Eight patients (11.43%) achieved a PR, while 51 patients (72.86%) experienced SD. The ORR of patients with LM and those with NLM were 7.8% and 21.0%, respectively. The DCR was 84.29% (n=59). The 1-year OS rate was 70.66%, and the 6-month PFS rate was 43.05% (*Table 2*). Of the 8 responding patients, 4 patients had liver metastases, 3 of whom were treated with local therapy for liver metastases.

We conducted univariate and multivariate Cox regression

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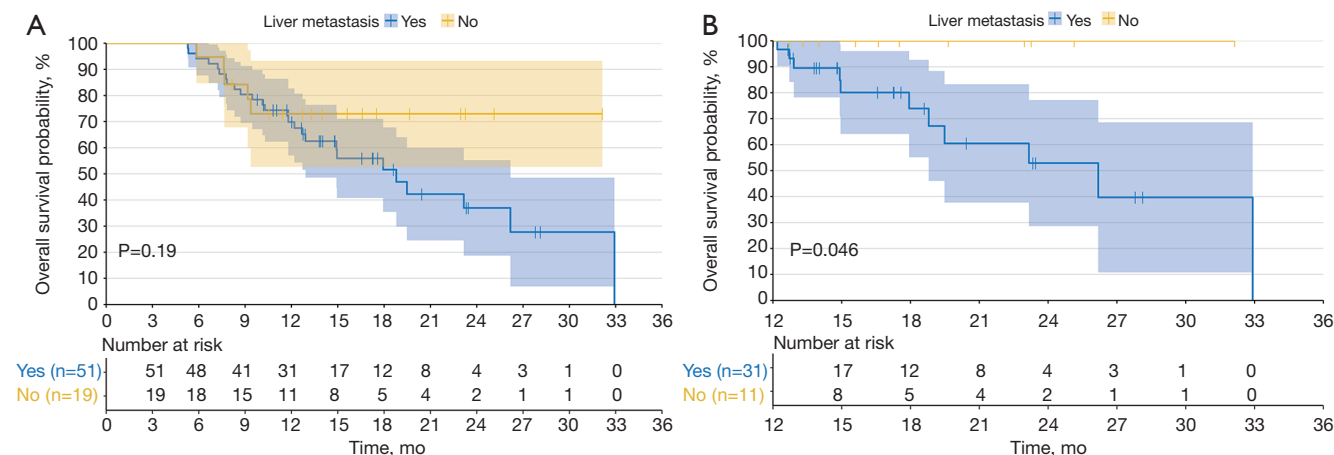
Figure 4 The KM-plot of overall survival (A); KM survival curve analysis at a landmark time point in overall survival (B). mo, month; KM, Kaplan-Meier.
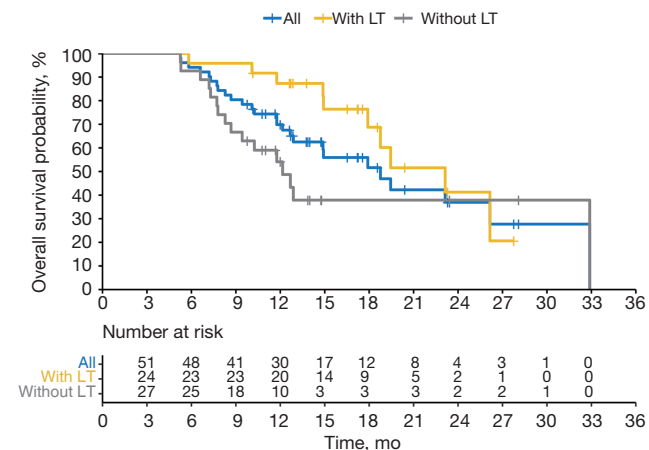
Figure 5 The KM-plot of overall survival in subset of liver metastasis. LT, local treatment; mo, month; KM, Kaplan-Meier.

Table 2 Efficacy

Outcomes	Estimate
CR	0
PR	8 (11.43)
SD	51 (72.86)
ORR	8 (11.43)
DCR	59 (84.29)
mOS (month)	19.48 (14.95–NA)
mPFS (month)	5.5 (4.30–6.77)
6-month PFS rate	43.05 (32.12–57.71)
1-year OS rate	70.66 (60.59–82.41)

Data are reported as No. (%) for counts, median (95% CI) for times, and percentage (95% CI) for rates. CR, complete response; PR, partial response; SD, stable disease; ORR, objective response rate; DCR, disease control rate; mOS, median overall survival; mPFS, median progression-free survival; PFS, progression-free survival; OS, overall survival; NA, not applicable; CI, confidence interval.

analysis to explore potential predictors for outcomes under this regimen. In univariate Cox regression for OS, LM without local treatment (HR =2.79, 95% CI: 1.01–7.74, P=0.049) showed a significant difference from NLM, whereas LM with local treatment (HR =1.26, 95% CI: 0.43–3.70, P=0.672) did not. Additionally, *KRAS* mutant (HR =2.85, 95% CI: 1.27–6.41, P=0.011) also indicated a significantly poor outcome. Based on the results of univariate analysis, OS did not exhibit significant differences concerning sex, age, primary lesion resection, or prior regorafenib treatment (P>0.05). For PFS, lung metastasis was a potential risk factor (HR =3.04, 95% CI: 1.36–6.81, P=0.007). Furthermore, multivariate Cox regression was

performed for adjusted results. Herein, LM without local treatment (HR =5.31, 95% CI: 1.33–21.31, P=0.0184) was still a risk factor for OS, whereas that with local treatment (HR =2.19, 95% CI: 0.55–8.69, P=0.263) was not. Besides, peritoneal and/or omentum metastasis, *KRAS* mutant, and low body mass index (BMI) were also identified as potential risk factors. Similar to the results from univariate Cox regression, lung metastasis was a potential risk factor for PFS (*Tables 3,4*).

Table 3 Cox regression for OS

Variable	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Male	0.94 (0.46–1.93)	0.864		
≥65 years	0.84 (0.32–2.22)	0.730		
LM with LT (*vs.* NLM)	1.26 (0.43–3.70)	0.672		
LM without LT (*vs.* NLM)	2.79 (1.01–7.74)	0.049	5.31 (1.33–21.31)	0.0184
Lung metastasis	1.19 (0.51–2.79)	0.683		
Peritoneal or omentum metastasis	1.09 (0.26–4.69)	0.904	8.08 (1.07–61.09)	0.0429
KRAS mutant	2.85 (1.27–6.41)	0.011	4.32 (1.62–11.53)	0.0035
Low BMI	2.12 (0.74–6.10)	0.164	8.14 (1.98–33.46)	0.0036
Primary lesion resected	0.60 (0.27–1.33)	0.211		
Lines ≥3	1.19 (0.53–2.69)	0.675		

OS, overall survival; HR, hazard ratio; CI, confidence interval; LM, liver metastasis; LT, local treatment; NLM, non-liver metastases; BMI, body mass index.

Table 4 Cox regression for PFS

Variable	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Male	1.06 (0.60–1.88)	0.847		
≥65 years	0.65 (0.29–1.48)	0.306		
LM with LT (*vs.* NLM)	1.25 (0.59–2.66)	0.554		
LM without LT (*vs.* NLM)	2.09 (0.95–4.60)	0.066		
Lung metastasis	3.04 (1.36–6.81)	0.007	8.77 (2.55–30.20)	0.0006
Peritoneal or omentum metastasis	0.91 (0.32–2.59)	0.863	6.24 (1.20–32.59)	0.0298
KRAS mutant	0.93 (0.51–1.68)	0.804		
Low BMI	0.85 (0.30–2.37)	0.754		
Primary lesion resected	0.68 (0.34–1.36)	0.275		
Lines ≥3	1.32 (0.71–2.47)	0.377		

PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; LM, liver metastasis; LT, local treatment; NLM, non-liver metastases; BMI, body mass index.

Safety

Out of the 70 patients, 61 (87.1%) had at least 1 TRAE and 6 (8.6%) patients had grade 3/4 TRAE (*Table 5*). The most common adverse events of all grades were hand-foot syndrome (37.14%, n=26), hypertension (34.29%, n=24), mucositis oral (32.86%, n=23), diarrhea (27.14%, n=19), and fatigue (17.14%, n=12). A total of 20 (28.5%) patients discontinued treatment due to TRAEs. The dose of fruquintinib was reduced in 4 cases. There were no deaths attributed to the treatment.

Discussion

There are currently few trials examining the effectiveness and safety of fruquintinib and PD-1 inhibitor in

Table 5 Adverse events

AEs	All grades, n (%)	Grade ≥3, n (%)
Hand-foot syndrome	26 (37.14)	2 (2.86)
Hypertension	24 (34.29)	0
Mucositis oral	23 (32.86)	0
Diarrhea	19 (27.14)	2 (2.86)
Fatigue	12 (17.14)	0
Autoimmune disorder	11 (15.71)	1 (1.43)
Liver dysfunction	9 (12.86)	1 (1.43)
Proteinuria	5 (7.14)	0
Hyperthyroidism	3 (4.29)	0
Hypothyroidism	1 (1.43)	0

AEs, adverse events.

combination. Here, we explored the efficacy and safety of fruquintinib in conjunction with anti-PD-1 therapy in MSS/pMMR mCRC patients as a late-line therapy. This study showed that the combination therapy resulted in a promising clinical outcome amongst Chinese patients diagnosed with mCRC, experiencing tumor progression after at least 2 prior chemotherapy regimens in real-world settings. the OS and PFS were 19.48 and 5.5 months, respectively. It is very similar to the results of a phase Ib/II prospective study that explored the safety and synergistic anti-tumor effect of fruquintinib in combination with sintilimab (an anti-PD-1 Ab) in patients with advanced CRC in the late-line therapy. In the 5 mg-intermittent cohort, the mPFS was 6.9 months, the mOS was 20.0 months (19), the ORR was 20%, and the DCR was 100%. In our study, the ORR and DCR were 11.43% and 84.29%, respectively. About 75.7% of the anti-PD-1 antibodies used in this study were sintilimab, and 18.6% of the patients used toripalimab. In two separate prospective, single-arm, single-center phase II clinical studies of fruquintinib combined with toripalimab, the median PFS was observed to be 5.98 and 6 months, respectively. The ORR were 21.5% and 16.7% (17,21). Yuan *et al.* conducted a phase 2 prospective study (FRUIT trial) and discovered that fruquintinib in combination with tislelizumab (an anti-PD-1 Ab) and SBRT was effective as a late-line treatment for MSS mCRC patients. The median PFS was 5.1 months, with an ORR of 26% and a DCR of 83% (18). Due to the short period of observation in these prospective studies, OS data have not yet been obtained. The ORR and

PFS of the above studies were improved compared with fruquintinib alone, which is consistent with our findings. In a retrospective trial, fruquintinib coupled with anti-PD-1 antibody resulted in an mPFS of 3.8 months and an mOS of 14.9 months in patients with resistant mCRC. The DCR was 62.2% (28/45) and ORR was 11.1% (5/45) (22).

Meta-analyses conducting indirect comparisons between fruquintinib and regorafenib revealed no significant differences in their efficacy and safety profiles (23,24). Nevertheless, there is an absence of head-to-head comparative clinical studies regarding their effectiveness. Usually patients can tolerate the recommended dose of 5 mg fruquintinib and rarely need dose reduction (25). On the contrary, most patients cannot tolerate the recommended dose of 160 mg when using regorafenib, and most of them start with 80 mg/120 mg in clinical practice (26).

Given that regorafenib is covered by medical insurance in China before fruquintinib, in this study, 40% of patients had used regorafenib in previous treatment, however there was no difference in PFS and OS compared with patients who did not use regorafenib. This is consistent with the conclusion of the FRECO2 study (25).

Previous studies have shown that LM is a poor prognostic factor in MSS/pMMR mCRC patients, and that patient with NLM derive clinical benefits from immune checkpoint inhibitors. In a retrospective study assessing the response rate (RR) and PFS to PD-1 or PD-L1 based therapy in patients with MSS mCRC, it was observed that NLM patients had significantly better PFS than those with LM (4 *vs.* 1.5 months; P<0.0001) (27). Another retrospective study aimed to evaluate the efficacy and safety of combining regorafenib or fruquintinib with sintilimab in patients with MSS mCRC. Subgroup analysis revealed that NLM patients responded more positively to this combined regimen than LM patients (ORR: 21.4% *vs.* 9.1%) and achieved improved OS (26 *vs.* 10.0 months, P=0.016) (28). Organ sites have exhibited differential responses, with lymph node and LM among the most and least responsive, respectively (29,30).

In the REGONIVO study, only 2 of 13 patients with LM showed objective response. In our study, we found that there was no statistically significant difference in OS between LM and NLM, but the NLM had numerically better survival, and the 2 survival curves diverged significantly after 1 year. Further analysis using the landmark method showed a statistically significant difference in OS between LM and NLM after 1 year, which is consistent with the long-tail effect of immunotherapy. We conducted a stratified analysis

on whether patients with LM received local treatment. The OS of patients with local treatment for LM was significantly better than that of patients without local treatment. Interestingly, there was no statistically significant difference in OS between patients with local treatment for LM and NLM. Multivariate Cox regression analysis showed that LM without local treatment is a poor prognostic factor for survival. As an organ with immunological tolerance, the liver might suppress both intrahepatic and extrahepatic immune responses in cancer patients. This suppression could be associated with reduced marginal CD8^{+} T-cell infiltration, potentially providing a mechanism for this outcome (30) Additionally, the liver is believed to be associated with a high proportion of immunosuppressive cells (31). Considering that these patients have extensive metastases, we believe that the reason why patients who received local treatment for LM alone had a significantly longer OS may be as follows: first, the liver is an important metabolic organ, and once LM lesions are not controlled, it may lead to abnormal liver function, jaundice, coagulation dysfunction, and other further effects on the patient's subsequent treatment. Secondly, local treatment for LM can not only delay the progression of local disease, but also lead to the production of new immune antigens, which can stimulate the function of immune cells and significantly enhance T-cell immune responses, resulting in stronger antitumor immunity and prolonged survival (32-34). Out of the 51 patients with LM, 4 responded to treatment, 3 of whom received local therapy for LM. Although LM is considered a poor prognostic factor and can predict suboptimal response to treatment, targeting the liver lesions with local therapy may potentially reverse this adverse factor.

Consistent with other studies, in our study, lung metastases were not a poor prognostic factor, although they adversely affected PFS. In the current study, all patients with lung metastases were accompanied with other site metastases that may confound their presumed response.

About half of patients with mCRC have a mutation in the *KRAS* oncogene, according to previous studies, it leads to a bad prognosis and a highly aggressive tumor biology. There was no statistically significant difference in PFS between patients with *KRAS* mutations and those with wild-type *KRAS*. This was consistent with the findings of Zhang *et al.* (35). However, this study has not yet determined the OS outcome due to insufficient follow-up time. In our study, *KRAS* mutation was a poor prognosis factor for OS.

This study has several limitations. Firstly, it was a single-center retrospective study, inherently prone to selection bias. Secondly, the utilization of 5 different anti-PD-1 antibodies affected the consistency of the treatment process. Thirdly, the relatively small sample size limits generalizability. Fourthly, the PD-L1 combined positive score (CPS) and tumor mutation burden (TMB) were not available, impeding the identification of the ideal population for immunosuppressant use. Lastly, the occurrence of the COVID-19 pandemic during the study period might have adversely influenced the study's outcomes. So far, all studies on the combination of anti-angiogenic drugs and PD-1 inhibitors have been small-sample phase I/II prospective or retrospective studies with single-arm designs. The conclusions are inconsistent, and there is a lack of double blind, randomized controlled phase III studies. The LEAP 017 study is the only ongoing phase III study (NCT04776148).

Conclusions

Combining fruquintinib with anti-PD-1 antibodies appears to be a viable and well-tolerated therapeutic strategy for patients with refractory MSS mCRC. Particularly in patients with LM, the inclusion of localized treatment notably extends patient survival. Further comprehensive research is essential to assess effectiveness and delineate the primary beneficiary population.

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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-23-931/rc

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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-23-931/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 independent ethics committee of the Hunan Cancer Hospital (No. 2023-55) and individual consent for this retrospective analysis was waived.

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