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Efficacy and safety of sintilimab plus bevacizumab and CAPOX as first-line treatment for patients with *RAS*-mutant, microsatellite stable, metastatic colorectal cancer

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Abstract

Background This research aimed to assess the efficacy and safety of combining sintilimab with bevacizumab, oxaliplatin, and capecitabine as a primary therapy for patients with RAS-mutated, microsatellite stable (MSS), and metastatic colorectal cancer (mCRC).

Methods In this prospective, open-label, single-arm, phase II trial, eligible patients received up to 8 cycles of capecitabine and oxaliplatin/bevacizumab plus sintilimab, followed by maintenance therapy with capecitabine, bevacizumab, and sintilimab every three weeks until disease progression. Treatment response was evaluated every 2 cycles (6 weeks) according to the Response Evaluation Criteria in Solid Tumors version 1.1. The primary endpoint was ORR, while the secondary endpoints included PFS and AEs.

Results The efficacy analysis and safety analysis included 33 patients. The overall response rate was 72.7%, and the median PFS in the full analysis set was 12.9 months (95% CI: 7.5–18.3), and median OS was not reached. Patients with liver metastases demonstrated a higher ORR (20/24 [83.3%]) than those without (4/9 [44.4%], $p=0.073$), and the median PFS was 14.7 for patients with liver metastases and 9.6 months for those without (HR: 1.05, 95%CI: 0.34–3.24; $p=0.932$). Most immune-related AEs had grades 1–2, and immunotherapy was discontinued in 4 patients due to immune-related AEs. No treatment-related deaths occurred during the study.

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Conclusions The therapeutic regimen showed encouraging antitumor effects and a favorable safety profile in patients with RAS mutations, MSS, and mCRC, yielding durable results throughout an extended follow-up duration, irrespective of the presence of liver metastases. This research is of great significance because it addresses the limited treatment options in the field of MSS mCRC patients. By providing new treatment strategies or methods, it brings more hope and choices to patients and offers valuable new insights and research directions to the medical community.

Clinical trial registration ClinicalTrials.gov: NCT06206096. Registered on May 26, 2021.

Keywords Microsatellite stable, Immune checkpoint inhibitor, Anti-angiogenesis, Metastatic colorectal cancer, Liver metastases

Introduction

Metastatic colorectal cancer (mCRC) is a leading cause of cancer-related morbidity and mortality worldwide [1]. The combination of fluorouracil, oxaliplatin, and/or irinotecan (CAPOX/FOLFOX/FOLFIRI) with bevacizumab is a first-line standard treatment option for mCRC patients with *RAS* mutation or microsatellite stability (MSS) [2, 3]. *RAS* mutations account for 50–55% of mCRC cases and are associated with poor prognosis [4, 5]. Furthermore, *RAS*-mutant mCRC exhibits an immunosuppressive microenvironment [6]. Despite significant improvements in clinical outcomes through optimized chemotherapy and targeted therapies, these therapies are still inadequate in delivering curative results for mCRC patients. Consequently, it is essential to explore novel strategies that specifically target the treatment of mCRC.

Over the past decade, significant progress has been made in the clinical treatment of a variety of solid tumors with the use of immune checkpoint inhibitors (ICIs), benefiting patients with malignancies such as melanoma, lung cancer, triple-negative breast cancer, advanced hepatocellular carcinoma, and microsatellite instability-high (MSI-H) metastatic colorectal cancer [7–10]. However, numerous clinical trials and case studies have indicated that immunotherapy has limited efficacy in treating colorectal cancer (CRC) [11]. Notably, MSS tumors are predominantly marked by immunosuppression or an immunologically "barren" condition, stemming from minimal or no T-cell infiltration and decreased expression of checkpoint molecules [12, 13]. Therefore, improving the efficacy of immunotherapy and exploring new mechanisms for MSS metastatic CRC treatment are crucial for enhancing the prognosis of cancer patients [14, 15].

Combining ICIs with anti-angiogenic drugs is a promising novel approach for cancer treatment [16, 17]. Anti-angiogenic treatment has the potential to alter the immunosuppressive tumor microenvironment by restoring blood vessel normalization, which in turn facilitates T-cell penetration and activation, and promots the efficacy of immunotherapy for solid tumors, including CRC [18]. Notably, numerous preclinical studies have confirmed the correlation between increased CD8 + T-cell infiltration and an enhanced antitumor immune response, as well as increased tumor cell death [19–21]. Therefore, the combination of ICIs and anti-angiogenic agents, which regulate the tumor microenvironment, can enhance and synergize with the antitumor immune response to ICIs [17].

However, limited data are available on combination therapies involving anti-angiogenic agents, chemotherapy, and immunotherapy, especially for the Chinese population. Furthermore, most Asians exhibit low tolerance to triple-drug chemotherapy regimens. In this study, a more tolerable two-drug chemotherapy regimen (capecitabine and oxaliplatin [CAPOX]) in combination with bevacizumab and sintilimab was selected as the first-line therapy for patients with *RAS*-mutant, MSS, and mCRC. This study was conducted to assess the safety and efficacy of this combination therapy and explore whether this treatment can effectively enhance antitumor immune responses, thereby paving the way for future randomized studies.

Materials and methods

Study design and participants

The present study was a prospective, open-label, single-arm, phase II trial conducted at the Fifth Medical Center of the Chinese People's Liberation Army General Hospital. The objective of this research was to assess the efficacy and safety of sintilimab in conjunction with CAPOX and bevacizumab as an initial therapy for patients with RAS-mutant, MSS, and mCRC.

The main eligibility criteria included the presence of histologically confirmed unresectable colorectal adenocarcinoma, a *RAS* mutation identified through genetic sequencing and MSS determined by polymerase chain reaction, age of 18–75 years, an Eastern Cooperative Oncology Group performance status of 0–1 [22], and adequate organ function. Patients who had received adjuvant or neoadjuvant chemotherapy or radiotherapy within six months before study enrollment were ineligible. In addition, patients with known *BRAF* mutations and *Her-2* positivity, uncontrolled hypertension despite

optimal drug treatment, active autoimmune diseases, or immunodeficiency were also excluded. Eligible mCRC patients underwent screening within 28 days prior to the start of treatment. The complete flow diagram of participants in the study is shown in Fig. 1.

Procedure

Patients who met the criteria were administered CAPOX/bevacizumab combined with sintilimab for a maximum of 8 cycles, followed by a maintenance regimen of capecitabine and bevacizumab, along with sintilimab, administered every three weeks until there was evidence of disease progression, intolerable toxicity, or a decision was made by either the patient or the physician. Bevacizumab was infused intravenously at a dose of 7.5 mg/kg every three weeks, and sintilimab, a recombinant, fully human IgG4 anti–PD-1 monoclonal antibody, was given at a dose of 200 mg via intravenous infusion with the same frequency; subsequently, oxaliplatin was administered every three weeks at a dose of 130 mg/m2, while

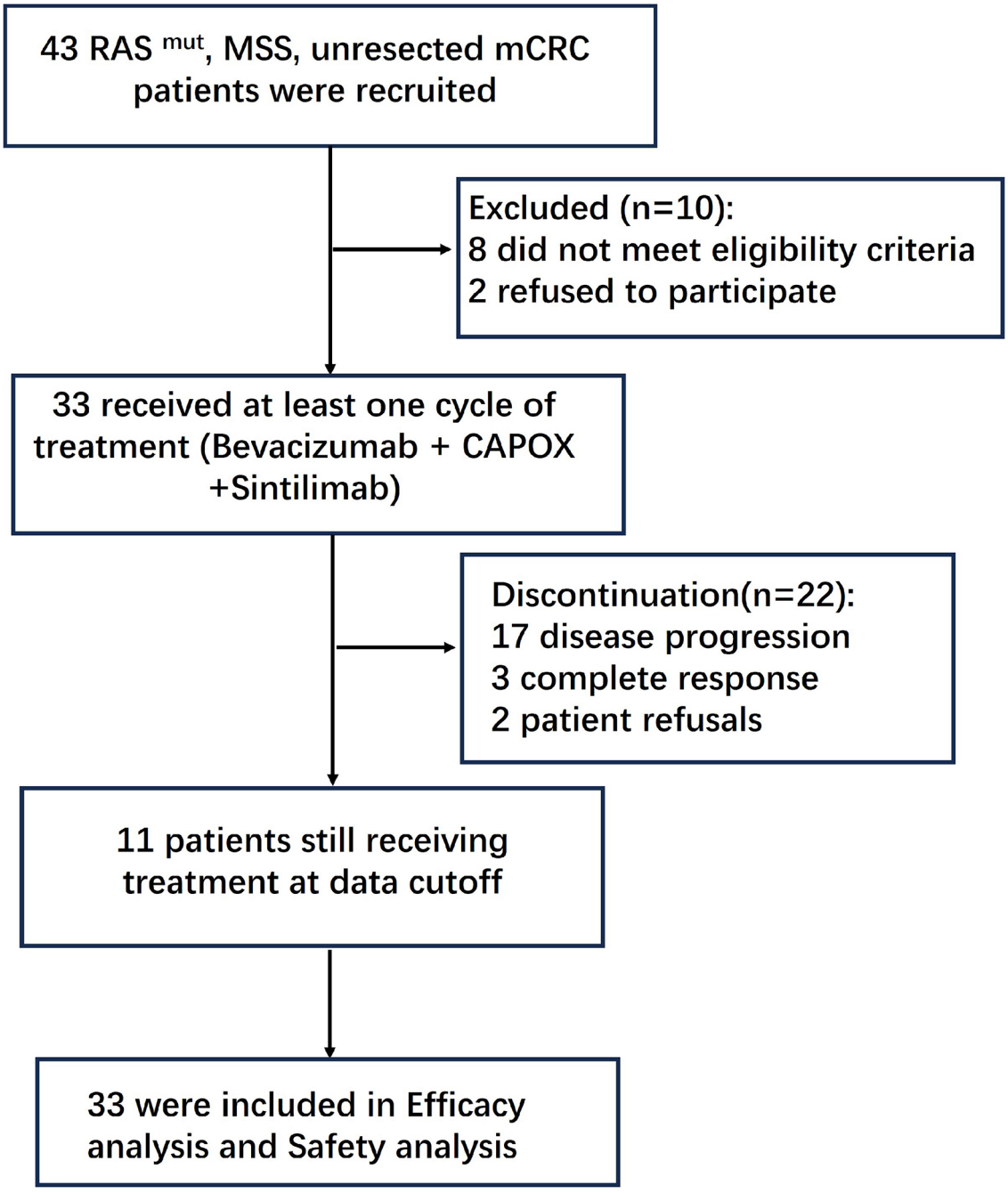

Fig. 1 Study flow diagram

capecitabine was taken orally at a dose of 1 g/m^2 twice daily for continuous oral administration over 14 days. The CAPOX regimen was selected due to its demonstrated efficacy and manageable toxicity profile in various clinical settings. Additionally, it offers the convenience of oral administration, which can improve patient compliance compared to other regimens that require intravenous infusion. We evaluated treatment response every two cycles (6 weeks) using computed tomography or magnetic resonance imaging according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (Fig. 2).

We evaluated the objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), and adverse events (AEs) for each patient. The primary endpoint was the investigator-assessed ORR, and the secondary endpoints were PFS and AEs. PFS was determined as the duration from the start of antineoplastic treatment to the initial record of tumor progression or death from any cause. The objective response rate (ORR) was determined by the percentage of patients who achieved either a complete response (CR) or a partial response (PR) as their best overall response. The disease control rate (DCR) was computed as the percentage of patients who reached a CR, PR, or stable disease as their optimal overall response. Patients who were alive and had no disease progression at the time of the last tumor assessment were censored.

AEs were summarized and categorized by the investigators using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0) [23] to determine potential associations with the study treatment. Immune-related AEs (irAEs) of grades 1–4, possibly related to the research regimen, were reported.

Statistical analysis

Based on an exact single-stage binomial design, a sample size of 30 patients with evaluable endpoints provided at least 80% power to detect an improvement in ORR from the historical report of 45–70% at a one-sided α level of 5% [24–26]. Considering a dropout rate of approximately 10%, the total sample size for this study was planned to be 33 patients. We conducted additional exploratory analysis to detect potential differences in treatment effects and prognosis between patients with and without liver metastases (LM), and the P value of the interaction was calculated to quantify the underlying effect.

PFS was estimated using the Kaplan–Meier method and compared using the Cox proportional risk model according to the presence of LM. PFS is presented as hazard ratios (HRs) with 95% confidence intervals (CIs). Statistical comparison of the ORR and DCR was performed using Fisher's exact test according to the presence of LM. Patient clinical baseline characteristics and safety data were summarized using descriptive statistics.

All patients who underwent at least one cycle of the research regimen were included in the full analysis and safety analysis. However, only those patients with assessable lesions were considered for the efficacy analysis. For the comparative analysis of PFS and ORR, a p-value ≤ 0.05

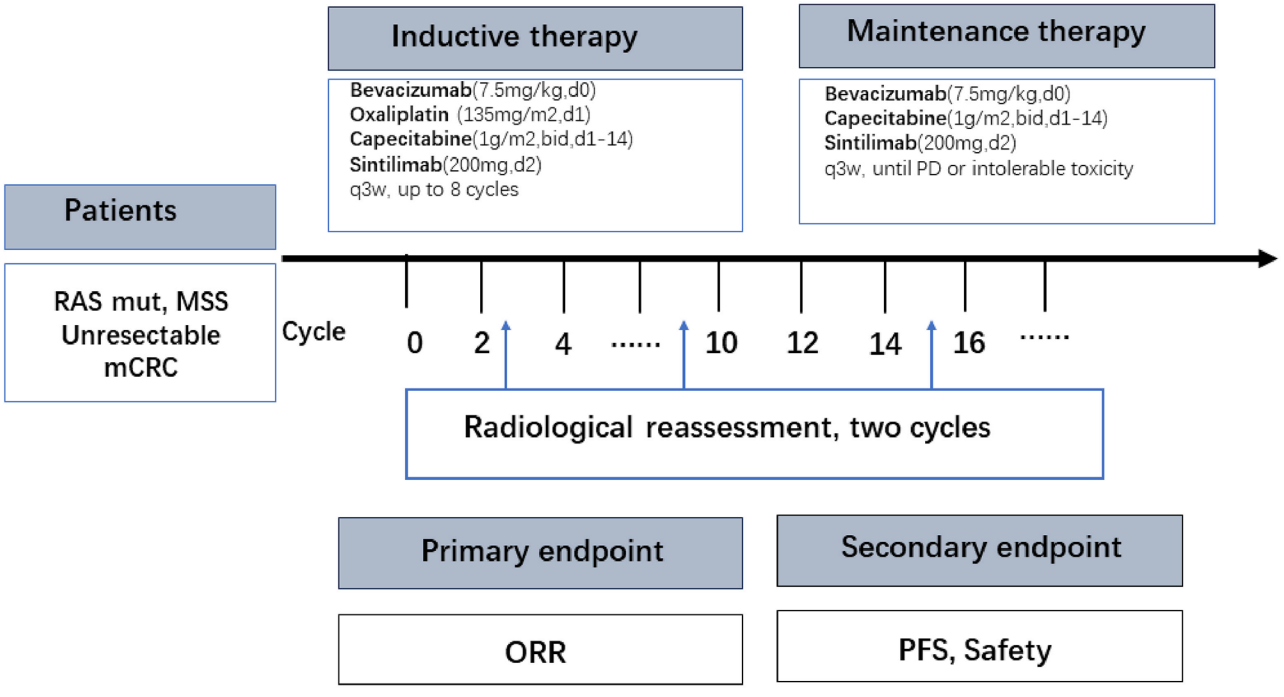

Fig. 2 Flowchart of participants in the study

was deemed statistically significant. Statistical analyses were conducted utilizing R version 4.2.3 and GraphPad Prism 10.

Results

Patient characteristics

Between January 1, 2021, and December 31, 2023, a total of 43 patients were screened for phase II clinical trials. Finally, 33 eligible patients were enrolled in this study. All patients received a minimum of one cycle and a maximum of eight cycles of protocol-specific therapy, followed by maintenance therapy. At the cutoff date (February 29, 2024), 11 patients were still receiving treatment, and the median follow-up period was 17.5 months (95% CI: 12.9 to 22.1 months).

Table 1 Baseline demographic and clinical characteristics

Characteristics	Patients ($n=33$)
Age, years, median (IQR), n (%)	57 (53–61)
< 60	22 (66.7%)
≥ 60	11 (33.3%)
Sex	
Female	17(51.5%)
Male	16 (48.5%)
ECOG performance status, n (%)	
0	12 (36.4%)
1	21 (63.6%)
Primary cancer site, n (%)	
Right colon	11 (33.3%)
Left colon	12 (36.4%)
rectum	10(30.3%)
Primary tumor resection, n (%)	
Yes	15(54.5%)
No	18(45.5%)
metastatic disease location, n (%)	
Liver	24 (72.7%)
Lung	10 (30.3%)
Lymph node	23 (69.7%)
Other	10 (30.3%)
Number of metastatic sites, n (%)	
≤ 2	22 (66.7%)
> 2	11 (33.3%)
***RAS*status, n (%)**	
KRAS	
codon 12	20(60.6%)
codon 13	5(15.2%)
codon 12 and 13	2 (6.1%)
NRAS	2 (6.1%)
Other	4 (12.1%)
PD-L1 expression, CPS, n (%)	
CPS ≤ 1	5 (15.2%)
CPS >1	4 (12.1%)
Unknown	24 (72.7%)
TMB (mut/Mb), n (%)	
TMB <5	4 (12.1%)
TMB ≥ 5	1 (3.1%)
Unknown	28(84.8%)

Abbreviations: CPS, Combined positive score; ECOG, Eastern Cooperative Oncology Group; IQR, Interquartile range; TMB, Tumor mutational burden; PD-1, Programmed cell death-1; PD-L1, Programmed cell death ligand-1

The demographics and baseline characteristics of participants are shown in Table 1. Patients had a median age of 57 years (IQR: 53–61). Among the 33 patients, 11 (33.3%) had right-sided tumors, 24 (72.7%) had hepatic metastasis, 27 (81.9%) had *KRAS* codon 12 or 13 mutant or comutant tumors, 2 (6.1%) had *NRAS* mutant tumors, and 14 (42.4%) underwent palliative surgery for primary tumor lesions. The efficacy analysis and safety analysis included all 33 patients. Among the 9 patients with available PD-L1 immunohistochemistry scores, 4 had a combined positive score > 1. Tumor mutation burden (TMB) data were available for five individuals; four patients had a TMB < 5 mut/Mb, while only one patient had a TMB ≥ 5 mut/Mb (TMB = 5.3 mut/MB).

Efficacy

Among the 33 patients with measurable disease at baseline, 4 (12.1%) achieved CR, and 20 (60.6%) achieved PR, resulting in an overall response rate of 72.7% (95%CI: 55.8-84.9%). In addition, 8 (24.2%) patients experienced disease stabilization, achieving a DCR of 96.9% (95%CI: 84.7-99.5%). The most significant percentage change in the diameter of the target lesion from the baseline among all patients and the liver metastasis group are depicted in Fig. 3A and B. On the cutoff day, 22 patients had progressive disease, 11 patients were still receiving treatment, and 6 patients had discontinued therapy (3 due to CR and 3 due to refusals) (Fig. 3C).

Moreover, among patients with LM ($n=24$), 3 (12.5%) had a CR, 17 (70.8%) had a PR, and 3 (12.5%) had stable diseases (Table 2). In the group without liver metastasis, one patient reached a CR, three patients achieved a PR, and five patients experienced SD. Patients with LM had a greater ORR (20/24, 83.3%) than those without LM (ORR: 4/9 [44.4%], $P=0.073$).

Survival

According to Kaplan–Meier estimations, the median PFS in the full analysis set was 12.9 months (95% CI: 7.5–18.3) (Fig. 4A), and median OS was not reached. The median PFS was 14.7 months (95% CI: 4.7–24.7) in patients with LM and 9.6 months (95% CI: 4.9–14.3) in patients without LM (HR: 1.05, 95% CI: 0.34–3.24, $p=0.932$; Fig. 4B). Among the 33 patients, 14 and 3 underwent palliative surgery for primary tumor lesions before and after the initiation of combination therapy, respectively, and 4 successfully attained CR status with the assistance of a multidisciplinary team. We conducted an exploratory subgroup analysis for PFS stratified by gender, age, ECOG, Primary cancer site, Liver metastasis, Lung

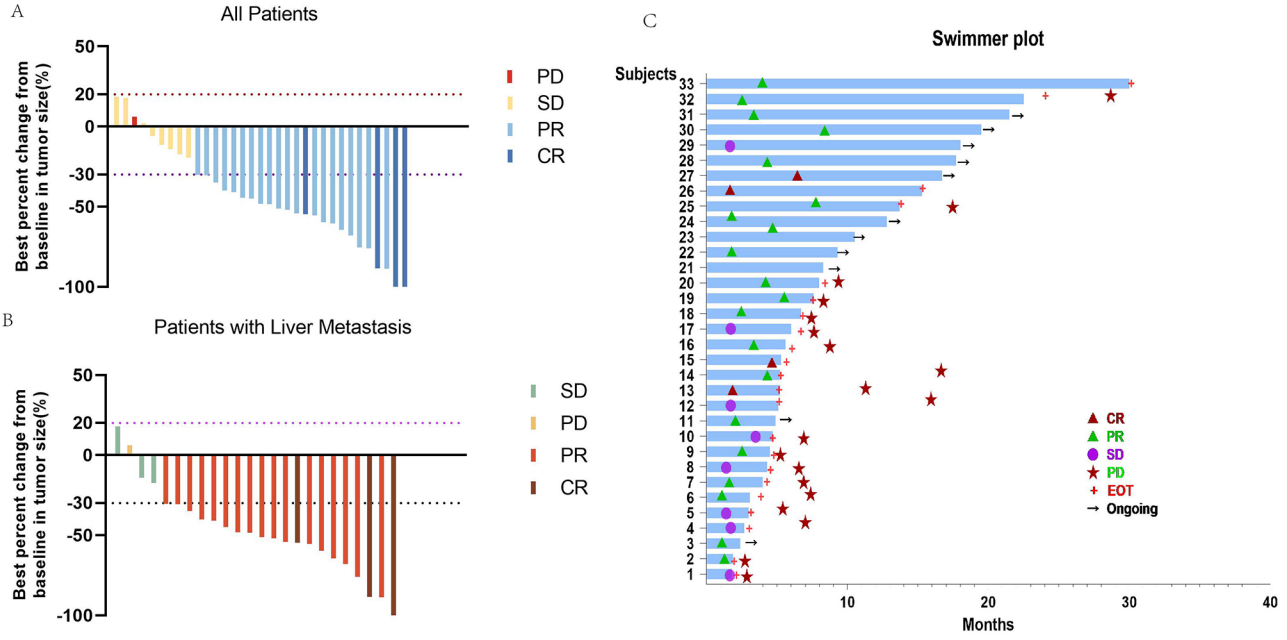

Fig. 3 (**A**) Waterfall plot of the maximum percent change in tumor size from baseline in all patients with measurable lesions (n=33). (**B**) Waterfall plot of the maximum percent change in tumor size from baseline in the liver metastates group (n=24). (**C**) Swimmer plots of all patients (n=33)

Table 2 Tumor response

	All patients($n=33$)	Liver metastases($n=24$)	Non-liver metastases($n=9$)
CR, (n)	4	3	1
PR, (n)	20	17	3
SD, (n)	8	3	5
PD, (n)	1	1	0
ORR, n (%)	24 (72.7%)	20 (83.3%)	4(44.4%)
DCR, n (%,)	32 (97.0%)	23 (95.8%)	9(100%)

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progress disease;

ORR, objective response rate; DCR, disease control rate

metastasis, Lymph node metastasis, Number of metastases, Primary tumor resection, Ras status, PD-L1 expression, and TMB. In our subgroup analysis, primary cancer site in left colon or rectal cancer and number of metastases ≤ 2 showed a significantly better prognosis (Fig. 5).

Safety

All 33 patients received at least one cycle of the protocol-specified treatment and were evaluated for safety. Overall, the treatment was shown to be well tolerated. Table 3 provides a summary of treatment-related adverse events (TRAEs) and irAEs. The most prevalent TRAEs of all grades were anemia (23/33, 70%), vomiting/nausea (16/33, 48%), neutropenia (15/33, 45%), neurological

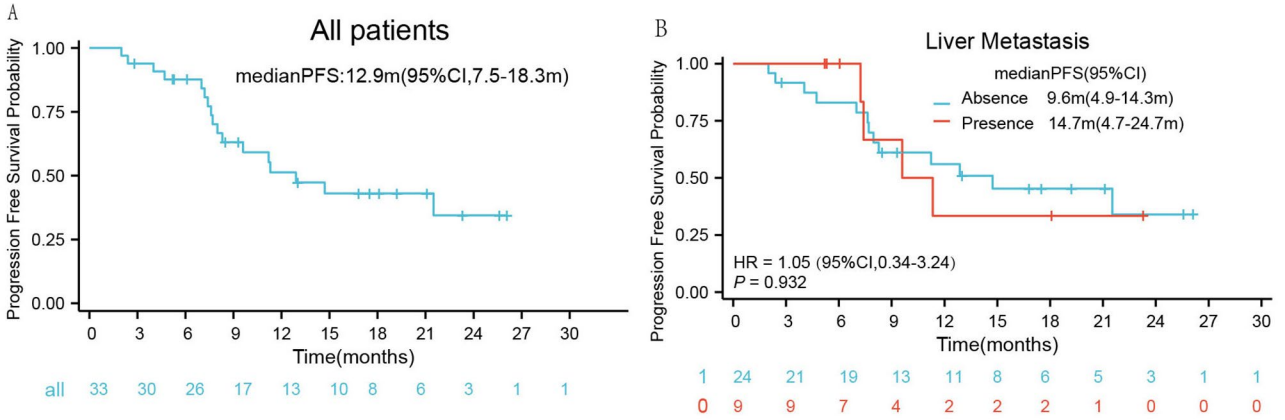

Fig. 4 (**A**) Kaplan-Meier curves of PFS for all patients. PFS: progression-free survival. (**B**) Kaplan-Meier curves of PFS according to the presence of liver metastates for all patients

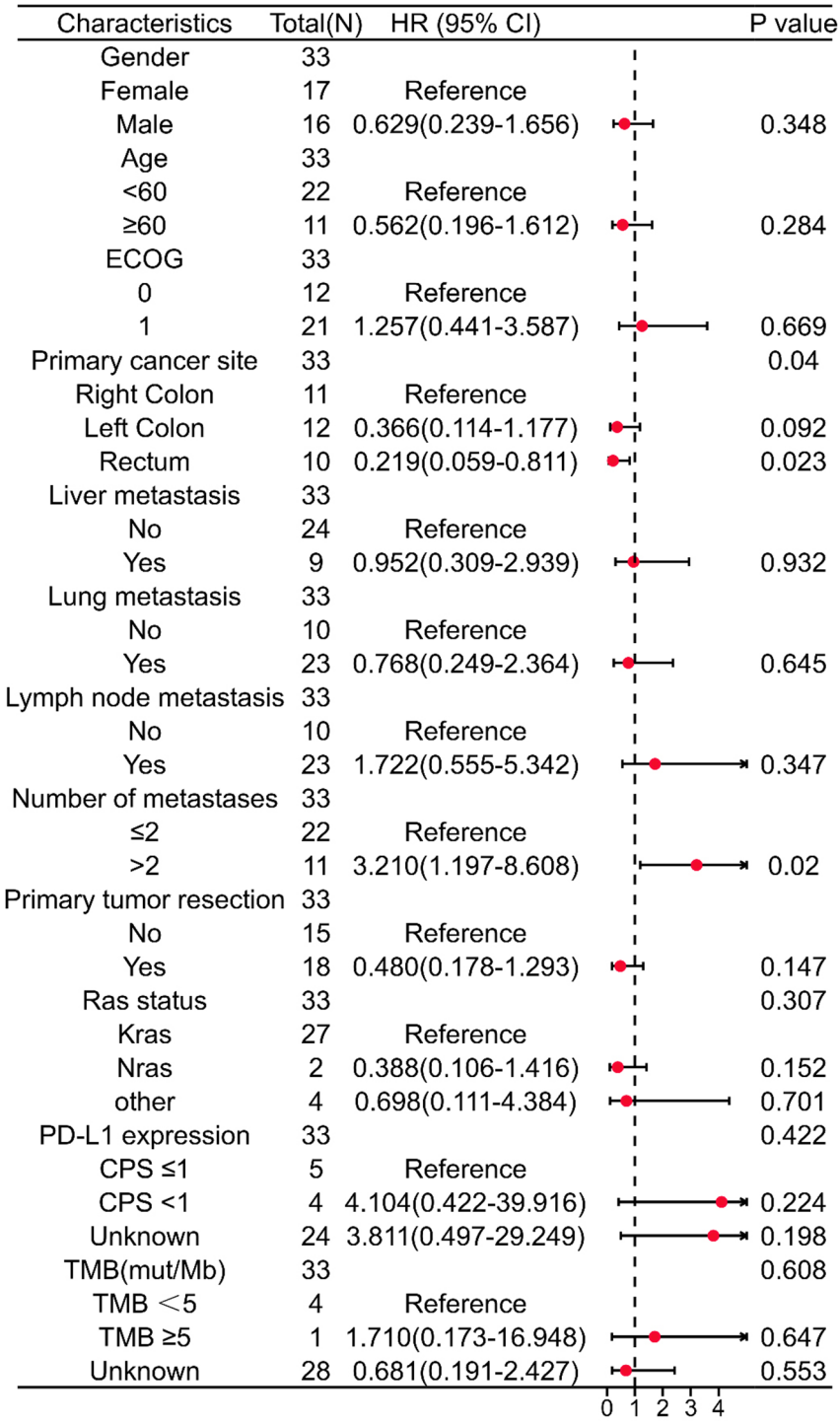

Fig. 5 Subgroup analyses for progressive-free survival in our study. Subgroups including gender, age, ECOG, Primary cancer site, Liver metastasis, Lung metastasis, Lymph node metastasis, Number of metastasis, Primary tumor resection, Ras status, PD-L1 expression, and TMB were analyzed. Abbreviations: ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed cell death-ligand 1; TMB, Tumaor Mutation Burden

toxicity (9/33, 27%), hand-foot syndrome (11/33, 33%), and fatigue (10/33, 30%). The most prevalent grade 3 or 4 TRAEs were Hand-foot syndrome (2/33, 6%) and transaminitis (2/33, 6%).

All-grade irAEs with potential immunologic etiology occurred in the following percentages of patients in the sintilimab combined with bevacizumab/CAPOX group: 12% (skin), 3% (gastrointestinal), 12% (lung), 9% (endocrine), and 9% (liver/pancreatic). Most irAEs had

Table 3 Treatment-related adverse events since the initiation of treatment

TRAEs, n(%)	Patients ($n=33$)				
	Any grade	Grade 1	Grade 2	Grade 3	Grade 4
Chemo-related adverse events					
Anemia	23(70%)	16(48%)	7(21%)	0	0
Vomiting/Nausea	16(48%)	11(33%)	5(15%)	0	0
Neutropenia	15(45%)	9(27%)	5(15%)	1(3%)	0
Hand-foot syndrome	11(33%)	7(21%)	2(6%)	2(6%)	0
Neurological toxicity	9(27%)	8(24%)	1(3%)	0	0
Fatigue	10(30%)	4(12%)	5(15%)	1(3%)	0
Hypertension	8(24%)	5(15%)	3(9%)	0	0
Transaminitis	8(24%)	4(12%)	2(6%)	2(6%)	0
Thrombocytopenia	5(15%)	2(6%)	2(6%)	1(3%)	0
Diarrhea	5(15%)	1(3%)	4(12%)	0	0
Constipation	4(12%)	2(6%)	2(6%)	0	0
Immune-related adverse events					
Skin toxicity	4(12%)	1(3%)	2(6%)	1(3%)	0
lung toxicity	4(12%)	1(3%)	3(9%)	0	0
Liver/Pancreas toxicity	3(9%)	1(3%)	1(3%)	1(3%)	0
Endocrine toxicity	3(9%)	1(3%)	2(6%)	0	0
Gastrointestinal toxicity	1(3%)	1(3%)	0	0	0
Any event leading to Discontinuation	4(12%)	0	2(6%)	2(6%)	0
Any event leading to death		0	0	0	0

grades 1–2, and immunotherapy was discontinued in four patients due to irAEs (two with pneumonia, one with hepatitis, and one with colitis). PD-1 inhibitors were reintroduced after the resolution of immune-related toxic effects in 2 patients with colitis and pneumonia. No deaths attributed to the treatment were reported throughout the course of the study. For managing these events, we follow established guidelines, which typically involve the use of immunosuppressive agents like steroids, with adjustments based on the severity and specific type of irAE.

Discussion

In this research, we evaluated the efficacy and safety of sintilimab plus bevacizumab in conjunction with CAPOX chemotherapy as the first-line treatment for patients with advanced CRC. To our knowledge, this study is the largest prospective trial to assess the combined efficacy of ICIs plus anti-angiogenic agents in combination with chemotherapy in previously untreated *RAS*-mutant, MSS, and metastatic CRC patients in China.

The combination of PD-1/PD-L1-targeting agents and anti-angiogenic drugs with standard doublet or triplet regimens has been explored in numerous clinical trials, yielding consistent results. Several clinical studies have confirmed the synergistic antitumor effects of this combination. AtezoTRIBE, a multicenter, open-label, randomized, controlled phase II study, suggested that the addition of atezolizumab to first-line FOLFOXIRI combined with bevacizumab may improve PFS in patients with mCRC while maintaining a good safety profile [13, 27]. It should be noted that patients in the AtezoTribe study were exclusively Italians, with PD-L1 monoclonal antibody selected as the treatment modality [13]. In addition, the NIVACOR trial, a phase II research study, was structured to evaluate the effectiveness and safety of nivolumab in conjunction with FOLFOXIRI/bevacizumab as a first-line therapy for patients with mCRC harboring *RAS*/*BRAF* mutations [28]. This clinical trial revealed that, regardless of *MMR* status, combination therapy showed promising efficacy in mCRC patients with *RAS/BRAF* mutations, with an acceptable toxicity profile [29]. Moreover, CheckMate 9×8 [30] evaluated the efficacy of NIVO + mFOLFOX6/BEV compared to mFOLFOX6/BEV as the first-line treatment for mCRC patients. Although the primary endpoint of this study, PFS, was not achieved, the combination of nivolumab and standard of care (SOC) demonstrated superior PFS rates, increased tumor response rates, and a longer duration of response than SOC at 12 months. Notably, patients with *KRAS* mutations who received nivolumab + SOC had longer PFS than those who received SOC (12.0 vs. 10.3, HR: 0.41, 95% CI: 0.17–0.96); the finding is consistent with that in our study. Furthermore, Xu et al. [31] compared serplulimab plus HLX04 and XELOX versus placebo plus bevacizumab and XELOX as first-line treatment for mCRC in a phase II/III study. They found that serplulimab plus HLX04 and XELOX significantly prolonged PFS, improved other efficacy endpoints, and demonstrated manageable safety. Similarly, patients with

KRAS mutations had better PFS than those in the control group (17.2 vs. 10.1, HR: 0.40, 95% CI: 0.17–0.95). *KRAS* status was a predictor for MSS, mCRC patients treated with PD-1 inhibitors plus XELOX and bevacizumab.

The combination of anti-angiogenic therapy and PD-1 monoclonal antibodies has shown encouraging effects on several types of tumors, including MSI-H CRC. However, this combination has limited benefits for *RAS* variant MSS mCRC patients with LM [32, 33]. The microenvironment of LM is reportedly associated with a relatively high proportion of immunosuppressive cells [34, 35]. Several studies have indicated that patients with LM exhibit a decreased response to immunotherapy, presumably due to the accumulation of immunosuppressive cells in LM [36–40]. A comparative analysis of the immune microenvironment between primary gastric tumors and LM was conducted using multiple immunohistochemistry (mIHC) [41]. Compared with primary gastric tumors, LM were found to contain a higher concentration of immunosuppressive cells, such as regulatory T cells, myeloid-derived suppressor cells, and tumor-associated macrophages, along with fewer CD8 + T cells, as revealed by mIHC. In this present study, we investigated the therapeutic outcomes of combined treatment with PD-1 antibodies and anti-angiogenic inhibitors for patients with or without LM. Our research proved that combination treatment with sintilimab, anti-angiogenic therapy, and chemotherapy was safe and efficient in previously untreated *RAS*-mutant, MSS, and mCRC patients. The ORR of 72.7% in all patients indicates a significantly higher proportion of patients experiencing tumor shrinkage or stabilization compared to the typical response rates observed with standard treatments. This suggests that our treatment approach may be more effective in controlling tumor growth and achieving clinical benefits for patients. The median PFS of 12.9 months represents a notable extension compared to the PFS typically seen with standard therapies. This longer duration of disease control can translate into improved quality of life for patients, as it allows them to maintain their daily activities and reduces the need for additional treatments or interventions during this period. Notably, patients with LM at treatment initiation seemed to have higher response rates than those without LM (ORR: 83.3% vs. 44.4.7%, $P = 0.073$). In addition, patients with LM exhibited a trend toward prolonged PFS compared to those without LM, although the difference did not reach statistical significance as determined by the log-rank test (PFS: 14.7 vs. 9.6 months, $P = 0.932$). The finding is consistent with results from a previous study in the first-line setting combined with chemotherapy [42]. This phenomenon is intriguing, and we hypothesize that the benefit could be attributed to the combination of chemotherapy with immunotherapy and anti-angiogenic therapy, as well as the transition from second-line therapy to first-line therapy. However, given the limited sample size of this study, it is not possible to draw definitive conclusions regarding the prediction of LM. It is necessary to explore the biological mechanisms underlying the differential response in patients with liver metastases more deeply. The liver's ability to promote immune tolerance can influence the response to treatments, as it can regulate systemic immune function and support metastatic seeding [43]. Besides, the interactions between tumor cells and the hepatic microenvironment, including immune cells such as Kupffer cells and hepatic stellate cells, can affect treatment outcomes [44]. Further fundamental research is necessary to determine the specific mechanisms involved.

To identify predictive biomarkers for combination therapy, several studies, including the REGONIVO study, are evaluating the association between immune-related or angiogenesis-related features of tumors and immunological determinants of clinical benefits. In the REGONIVO study with a limited number of CRC patients, exploratory analysis revealed no clear relationship between PD-L1 expression or TMB and treatment outcomes [45]. The analysis of additional biomarkers using pre- and post-treatment biopsy samples is still ongoing to elucidate the immunological effects of this combination. In addition, Yuan et al. conducted a phase II study of combination treatment with sintilimab plus bevacizumab/CAPOX as the first-line treatment in *RAS*-mutant, MSS, and unresectable mCRC patients [42]. They found no significant differences in *RAS* mutation types, TMB or PD-L1 expression between patients with CR/PR and those without. Additional investigations with a larger sample size are crucial to elucidate the impact of these clinical factors on the effectiveness of combination therapy.

This study has several limitations. First, the primary limitation of this study was its small sample size and single-arm nature, necessitating confirmation of the results through phase III randomized controlled trials with stratified subgroups based on factors such as the presence of liver metastases and other relevant biomarkers. Small sample sizes can compromise a study's ability to detect even moderate or small effects, leading to underestimation of treatment effectiveness and highly variable results that are sensitive to outliers. Despite these limitations, findings can still provide valuable insights for clinical decision-making, suggesting areas for further exploration. To enhance future research, it's crucial to consider statistical power in study design, promoting collaboration and data sharing to increase sample sizes and improve the generalizability of results. Second, we only summarized the clinical efficacy, survival, and safety data. Thus, some of our findings need further validation through additional basic research. Additionally, we did

not perform an exploratory analysis of potential biomarkers to forecast the efficacy of combination therapy.

Conclusions

The combination of CAPOX/bevacizumab plus sintilimab as a first-line therapy showed promising antitumor efficacy and a favorable safety profile for *RAS*-mutant, MSS, and mCRC patients, with enduring positive results over an extended follow-up period, regardless of LM. More extensive basic research with a larger sample size is needed to elucidate the mechanisms underlying the enhanced treatment efficacy observed in patients with LM.

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Author contributions
GHD, ZKW and QLH contributed to the conception and design of the study. YRW, RJ, HYS, YM, MJF, FFL, YS, YSJ, and YYZ contributed to the data collection, analysis and interpretation. YRW and RJ contributed to manuscript preparation, editing and review. All authors reviewed and approved the final submitted manuscript.

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Data availability
Due to patient privacy and consent restrictions, the clinical trial data provided in this article have not been made publicly available. However, interested parties can obtain the data by contacting the corresponding author upon reasonable request. The use of the data must comply with the requirements set by China's Department of Human Genetic Resources Management and specific regulations in other countries or regions.

Declarations

Ethics approval and consent to participate
The protocol was approved by the Ethics Committee of the Chinese PLA General Hospital (S2020-530-02). This study was conducted in accordance with the Helsinki Declaration. Written informed consent forms regarding the research procedures were obtained from all patients prior to their enrollment.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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