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ORIGINAL ARTICLE

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Phase Ib study of anti-EGFR antibody (SCT200) in combination with anti-PD-1 antibody (SCT-I10A) for patients with RAS/BRAF wild-type metastatic colorectal cancer

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ABSTRACT

Objective: This study evaluated the safety and efficacy of an anti-epidermal growth factor receptor (EGFR) antibody (SCT200) and an anti-programmed cell death 1 (PD-1) antibody (SCT-I10A) as third-line or subsequent therapies in patients with rat sarcoma viral oncogene (RAS)/v-raf murine sarcoma viral oncogene homolog B (BRAF) wild-type (wt) metastatic colorectal cancer (mCRC).

Methods: We conducted a multicenter, open-label, phase Ib clinical trial. Patients with histologically confirmed RAS/BRAF wt mCRC with more than two lines of treatment were enrolled and treated with SCT-I10A and SCT200. The primary endpoints were the objective response rate (ORR) and safety. The secondary endpoints included disease control rate (DCR), progression-free survival (PFS), and overall survival (OS).

Results: Twenty-one patients were enrolled in the study through January 28, 2023. The ORR was 28.57% and the DCR was 85.71% (18/21). The median PFS and OS were 4.14 and 12.84 months, respectively. The treatment-related adverse events (TRAEs) were tolerable. Moreover, compared with the monotherapy cohort from our previous phase I study evaluating SCT200 for RAS/BRAF wt mCRC in a third-line setting, no significant improvements in PFS and OS were observed in the combination group.

Conclusions: SCT200 combined with SCT-I10A demonstrated promising efficacy in previously treated RAS/BRAF wt mCRC patients with an acceptable safety profile. Further head-to-head studies with larger sample sizes are needed to validate whether the efficacy and safety of combined anti-EGFR and anti-PD-1 therapy are superior to anti-EGFR monotherapy in the third-line setting. (Registration No. NCT04229537).

KEYWORDS Colorectal cancer; SCT-I10A; SCT200; epidermal growth factor receptor; programmed cell death 1

Introduction

Colorectal cancer (CRC) is one of the most prevalent malignancies worldwide, ranking third among all malignant tumors and the second most frequent cause of cancer-related death[1]. Chemotherapy remains the major treatment option for metastatic colorectal cancer (mCRC) with a median overall survival (OS) of 16–23 months[2,3]. The survival time of patients with

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mCRC has gradually improved in recent decades[4]. Targeted therapy has greatly improved patient survival. The addition of a targeted regimen with traditional chemotherapy has resulted in a median OS of 29–30 months in the first line[5]. However, for patients who have failed front-line treatment, the prognosis remains poor. Tyrosine kinase inhibitors (regorafenib and fruquinitinib) and oral chemotherapy drugs (TAS-102) are currently recommended as third-line therapies but the survival benefits are limited[6-9].

The last decade has witnessed the explosive development of immune checkpoint inhibitor-based immunotherapies, such as programmed cell death 1 (PD-1)/programmed cell death 1 ligand 1 (PD-L1) inhibitors in cancer therapy. A satisfactory clinical response has been observed in mismatch repair deficiency (dMMR) or microsatellite instability-high (MSI-H) CRC patients[10-12], which account for only 5% of mCRC cases. For the remaining 95% of patients with mismatch repair proficiency (pMMR) or microsatellite stability (MSS), limited survival benefits were observed[13], possibly due to the lack of immune infiltration and low tumor mutation burden (TMB)[14]. Several studies have identified a variety of factors, such as tumor immunogenicity, T cell function, PD-L1 expression, and the tumor microenvironment, as possible contributors to clinical responses during PD-1/PD-L1 blockade[14,15]. These findings provide valuable insight for the development of combinatorial strategies to enhance the efficacy of immunotherapy in patients with mCRC.

The epidermal growth factor receptor (EGFR) is an important therapeutic target for rat sarcoma viral oncogene (RAS)/v-raf murine sarcoma viral oncogene homolog B (BRAF) wild-type (wt) mCRC. The survival benefits of anti-EGFR monoclonal antibodies (mAbs) in patients with RAS/BRAF wt mCRC across all lines of treatment have been verified in phase III studies[16-21]; however, some patients develop resistance to anti-EGFR mAbs after 7–10 months of treatment. The molecular mechanisms underlying intrinsic or acquired resistance have been explored in RAS wt mCRC[22,23]. During anti-EGFR therapy, cancer cells harboring RAS mutations undergo genetic selection and become dominant in the tumor tissues, leading to therapy resistance and disease progression[24]. It has also been shown that discontinuation of anti-EGFR therapy partially restores the activity of RAS wt cells, indicating that anti-EGFR mAb rechallenge may be effective in patients developing acquired resistance[25]. Therefore, anti-EGFR mAbs have a promising application in RAS/BRAF wt mCRC, including patients who develop resistance to previous anti-EGFR-based therapy.

The EGFR signaling pathway is closely associated with the tumor immune microenvironment (TIM)[26,27]. For example, the Fc region of cetuximab binds to the Fc receptor on natural killer (NK) cells, thereby mediating antibody-dependent cell-mediated cytotoxicity (ADCC) and inducing innate immunity[28]. Blocking the EGFR pathway also modulates immune infiltration and activates antitumor activity of the immune system[26,29]. Moreover, cetuximab contributes to the immunosuppressive tumor microenvironment by upregulating the expression of immune checkpoints and infiltration of Treg cells *via* negative feedback regulation. These findings provide a rationale for combining anti-EGFR reagents with immunotherapy[30]. Anti-EGFR therapy increases the expression of major histocompatibility complex (MHC) class II molecules and the recruitment of T cells in the TIM, which promotes transformation of the TIM from a "cold" phenotype to a "hot" phenotype[31]. Therefore, anti-EGFR therapy may exert synergistic effects with immunotherapy. In fact, combining anti-EGFR targeted therapy with immunotherapy has shown great promise in pretreated RAS wt mCRC patients with good antitumor activity and manageable safety[32,33].

SCT200, a recombinant human EGFR monoclonal antibody, specifically binds to EGFR with low immunogenicity. Therefore, SCT200 is suitable for long-term clinical treatment. Notably, SCT200 exerts a significantly stronger ADCC effect *via* its specially designed Fc domain. SCT-I10A, a humanized mAb, restores the antitumor activity of T cells by blocking PD-1 binding to its ligand. In a preliminary clinical trial, SCT200 monotherapy demonstrated strong antitumor activity and controllable safety, with an objective response rate (ORR) of 30.4% and a disease control rate (DCR) of 69.6% in chemotherapy-refractory mCRC[34]. Inspired by the breakthrough of anti-EGFR therapy plus immunotherapy in mCRC, we designed a phase Ib trial to evaluate the safety and efficacy of SCT-I10A in combination with SCT200 as a third-line or subsequent treatment in patients with mCRC.

Materials and methods

Study design

This was a multicenter, open, phase Ib clinical trial to evaluate the safety and efficacy of SCT-I10A combined with SCT200 as third-line or subsequent therapy in patients with mCRC (ClinicalTrials.gov identifier: No. NCT04229537). The primary endpoints of safety assessment were the incidence and severity of all adverse events (AEs), treatment emerged adverse

events (TEAEs), treatment-related adverse events (TRAEs), immune-related adverse events (irAEs), and serious adverse events (SAEs). The primary endpoint of the efficacy assessment was the ORR according to the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1). Secondary endpoints included DCR, duration of response (DOR), progression-free survival (PFS), OS, and immunogenicity.

This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. For prospective patients, the potential benefits and risks of the clinical trial were described in detail and informed consent was obtained. This study was approved by the Ethics Committee of each participating institute.

Patient eligibility

Patients who met the following inclusion criteria were included in this study: (1) histologically confirmed RAS/BRAF wt mCRC; (2) 18–75 years of age; (3) Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1; (4) refractory or intolerant to two or more chemotherapy regimens (fluorouracil, oxaliplatin, or irinotecan); (5) optimal partial response (PR) if treated with anti-EGFR therapy previously; (6) at least one measurable lesion according to RECIST version 1.1; (7) full organ and bone marrow function [absolute neutrophil count $\geq 1.5 \times 10^9$/L; platelet count $\geq 100 \times 10^9$ /L; hemoglobin ≥ 90 g/L or 5.59 mmol/L; plasma creatinine $\leq 1.5 \times$ upper limit normal (ULN) or creatinine clearance rate ≥ 60 mL/min; alanine aminotransferase (ALT) and aspartate aminotransferase (AST) $\leq 3 \times$ ULN; if there was liver metastasis, ALT and AST $\leq 5 \times$ ULN, total bilirubin $\leq 1.5 \times$ ULN; if direct bilirubin $> 1.5 \times$ ULN, ALT and AST $\leq 1.5 \times$ ULN]; and (8) expected survival time > 3 months.

The exclusion criteria were as follows: (1) allergic to SCI-I10A or SCT200; (2) the last treatment regimen before enrollment contained anti-EGFR drugs; (3) previously received anti-PD-1/PD-L1 therapy; (4) active autoimmune diseases or a history of autoimmune diseases; and (5) diagnosed with other malignancies within 5 years, except effectively treated basal cell carcinoma of the skin, squamous cell carcinoma of the skin, and effectively resected cervical or breast cancer.

Procedures

Patients who met the inclusion criteria after screening were enrolled in this study and administered SCT200 plus SCT-I10A. SCT-I10A was administered *via* an intravenous infusion at a dose of 200 mg once every 3 weeks, whereas SCT200 was administered *via* an intravenous infusion at 6.0 mg/kg once a week for 12 weeks, followed by 8.0 mg/kg once every 2 weeks. Patients continued to receive investigational drugs until progressive disease (PD), intolerable toxicity, new antitumor therapy, or a deliberate decision by patients or investigators to terminate treatment, death, or lost to follow-up. For patients with PD according to RECIST v1.1, if the clinical symptoms were stable, medication was continued if judged to be clinically beneficial at the discretion of the researcher and with patient consent. The duration of treatment with medication was ≤ 2 years.

Assessment

Enhanced computed tomography (CT) or magnetic resonance imaging (MRI) was used for antitumor response evaluation. A baseline tumor assessment was performed within 28 days prior to the initial treatment. Subsequent evaluations of the antitumor response were performed every 6 weeks from the initial administration until disease progression whether or not a delay in the treatment cycle occurred. Patients who achieved initial disease remission, including a complete response (CR) or PR, underwent imaging examinations 4–8 weeks after the initial tumor evaluation for further confirmation. Patients who received at least one treatment cycle were included in the safety analysis. Safety evaluations were performed every 6 weeks from the first administration of medications. Immunogenicity was defined as the number and percentage of patients who tested positive for anti-drug antibodies (ADAs) against SCT-I10A or SCT200. Blood samples were collected within 7 days before the initial administration, at week 7 ($\pm$ 3 days), every 12 weeks starting at week 7 ($\pm$ 3 days), and at the end of treatment visits. The expression of PD-L1 was assessed using the PD-L1 immunohistochemistry 22C3 pharmDx assay (Agilent Technologies, Carpinteria, CA, USA).

SCT200 monotherapy cohort

The safety, tolerability, and efficacy of SCT200 monotherapy in patients with KRAS/NRAS/BRAF wt mCRC were previously investigated in a phase I clinical trial (ClinicalTrials.gov identifier: No. NCT02211443). The patients and methods of the SCT200 monotherapy cohort were elucidated in a previously

published article[34]. The efficacy and safety data were collected from a dose-expansion cohort.

Statistical analysis

The primary analysis was performed after the last patient completed at least two efficacy assessments. Data from the different centers that participated in this clinical trial were included in the final analysis. Demographic and baseline characteristics were described using corresponding statistics based on the data type. The Kaplan-Meier method was used to evaluate the OS, PFS, and DOR median and 95% confidence interval (CI), and survival curves were drawn. The ORR and DCR are summarized descriptively. Descriptive statistics were used to summarize the main safety data, including the incidence of AEs, TEAEs, TRAEs, irAEs, and SAEs. Statistical analyses were performed using SAS 9.4 software.

Results

Baseline characteristics

A total of 30 patients were screened between August 2020 and September 2022. Twenty-one patients met the inclusion criteria and were enrolled (**Figure 1**). The baseline characteristics of the enrolled patients are summarized in **Table 1**. The median patient age was 58 years (range, 32–70 years), 52.4% (11/21) were male, and 28.6% (6/21) had an ECOG PS of 0. Sixteen patients had primary tumors located on the left side or rectum and five patients had primary tumors located on the right half of the colon. Six patients had tumors in more than three metastatic organs. Although data regarding PD-L1 expression were not required per the inclusion criteria, all patients were tested for PD-L1 expression. All patients (21/21) had a PD-L1 combined positive score (CPS) < 10 or a PD-L1 tumor proportion score (TPS) < 1%; 4 patients [4/21 (19%)] had a PD-L1 CPS ≥ 1. No MSI-H or dMMR types were detected in any of the enrolled patients. Four patients (19%) had already received at least 5 rounds of previous therapy. Seven patients (33.3%) had been previously treated with cetuximab, and the time between the end of anti-EGFR treatment and the start of this clinical trial was ≥ 6 months in these patients. The median duration of follow-up was 27.1 months, and the median number of treatment cycles was 18.1 for SCT-I10A and 18.0 for SCT200.

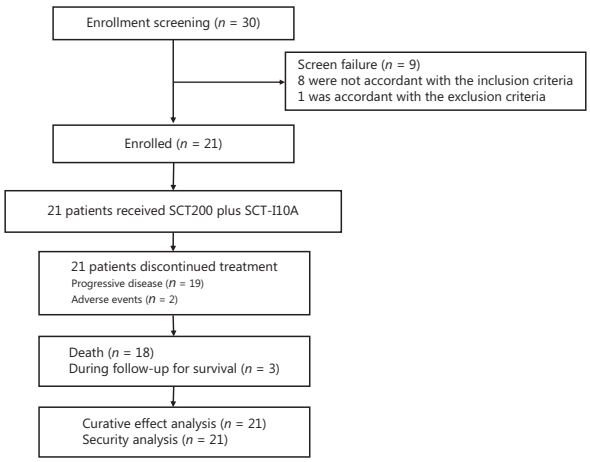


Figure 1 Flowchart of the trial design.

Antitumor activity

Twenty-one patients were eligible and assessed for efficacy endpoints (**Table 2**). Among these patients, 6 achieved PR with no CR observed and the ORR was 28.57%. Stable disease (SD) was achieved in 12 patients with a DCR of 85.71% (18/21). The median OS was 12.84 months (95% CI, 6.64–16.06 months) and the 12-month OS rate was 57.10%. The median PFS was 4.14 months (95% CI, 2.73–5.45 months) and the 6-month PFS rate was 16.71%. The median DOR was 2.87 months [95% CI, 1.54 months (not reached)].

We grouped patients according to their clinical characteristics and analyzed the efficacy of the SCT200 plus SCT-I10A regimen (**Supplementary Table S1**). The clinical benefits of SCT200 plus SCT-I10A have also been observed in patients who have received at least 5 rounds of previous therapies. Although the ORR was slightly higher in patients with liver metastasis than in those without, the OS was longer in patients with no liver metastasis. Notably, patients who previously received cetuximab experienced lower clinical benefits than those who did not.

Safety

For the safety evaluation, we summarized the grade and impact of AEs (**Supplementary Table S2**). All patients in this study had TEAEs and TRAEs. Treatment suspension was required in five patients, which was attributed to SCT-I10A-associated TRAEs, and one patient discontinued medication because of a TRAE (hypophysitis) related to SCT-I10A. Nine patients

Table 1 Baseline characteristics of patients with colorectal cancer

Characteristic	Patients (*n* = 21)
Age	
Median age (years, range)	58 (32, 70)
< 65, *n* (%)	14 (66.7)
≥ 65, *n* (%)	7 (33.3)
Gender, *n* (%)	
Male	11 (52.4)
Female	10 (47.6)
ECOG PS, *n* (%)	
0	6 (28.6)
1	15 (71.4)
Location of the primary tumor, *n* (%)	
Left-side colon or rectum	16 (76.2)
Right-side colon	5 (23.8)
Number of organs with metastases, *n* (%)	
0	0
1	7 (33.3)
2	8 (38.1)
≥ 3	6 (28.6)
Expression of PD-L1, *n* (%)	
CPS < 1	17 (81.0)
1 ≤ CPS < 10	4 (19.0)
CPS ≥ 10	0
TPS < 1%	21 (100.0)
TPS ≥ 1%	0
Treatment lines, *n* (%)	
3L	12 (57.1)
4L	5 (23.8)
≥ 5L	4 (19.0)
Previous cetuximab therapy, *n* (%)	
Yes	7 (33.3)
No	14 (66.7)

n, number; ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed cell death ligand 1; CPS, combined positive score; TPS, tumor proportion score.

experienced drug interruption due to SCT200-associated TRAEs, and one patient discontinued medication because of a TRAE related to SCT200 (acne-like dermatitis).

Table 2 Efficacy endpoints of SCT200 plus SCT-I10A cohort and SCT200 cohort

Characteristic	SCT200 + SCT-I10A
Number of patients	21
Best tumor response, *n* (%)	
PR, *n* (%)	6 (28.57)
SD, *n* (%)	12 (57.14)
PD, *n* (%)	3 (14.29)
ORR, *n* (%)	6 (28.57)
DCR, *n* (%)	18 (85.71)
OS, median (95% CI), months	12.84 (6.64, 16.06)
PFS, median (95% CI), months	4.14 (2.73, 5.45)
DOR, median (95% CI), months	2.87 (1.54, NA)

n, number; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate; PFS, progression-free survival; OS, overall survival; DOR, duration of response; NA, not available.

TRAEs were reported in all patients; however, most of the events were grade 1 or 2 and manageable, thus posing no significant safety concerns. The most common TRAEs were hypomagnesemia [16/21 (76.2%)], rash [10/21 (47.6%)], acneiform dermatitis [9/21 (42.9%)], proteinuria [8/21 (38.1%)], elevated blood alkaline phosphatase levels [4/21 (19%)], and hyperthyroidism [4/21 (19%)]. Grade 3 or 4 TRAEs, occurring in 52.4% (11/21) of the patients, were mainly hypomagnesemia [7/21 (33.3%)], rashes [2/21 (9.5%)], acneiform dermatitis [2/21 (9.5%)], immune-mediated dermatitis [1/21 (4.8%)], atopic dermatitis [1/21 (4.8%)], hypokalemia [1/21 (4.8%)], increased creatine phosphokinase [1/21 (4.8%)], increased myoglobin levels [1/21 (4.8%)], and skin infection [1/21 (4.8%)]. No grade 5 TRAEs were observed during treatment (**Table 3**).

Immunogenicity

The immunogenicity of SCT-I10A and SCT200 was evaluated in 21 patients. Preliminary results showed that 1 patient (4.8%) was positive for anti-SCT-I10A antibodies at baseline, although additional verification was needed. All patients tested negative for anti-SCT-I10A antibodies during treatment and anti-SCT200 antibodies at baseline and during treatment.

Table 3 Summary of any-grade TRAEs occurring in ≥ 5% of patients and all TRAEs of grade 3 or 4

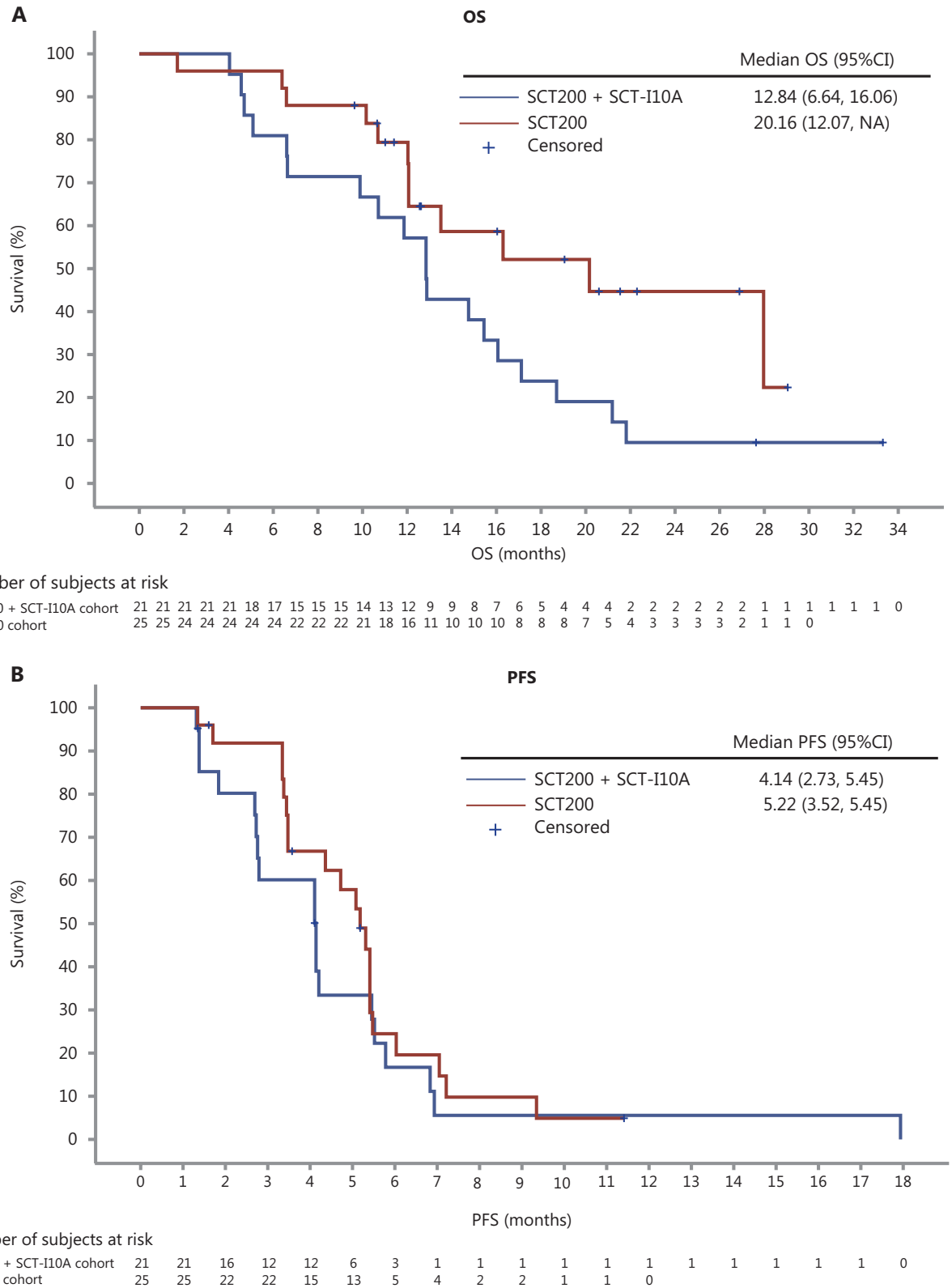
Adverse event	Any grade *n* (%)	Grade 1 or 2 *n* (%)	Grade 3 or 4 *n* (%)
All	21 (100.0)	21 (100.0)	11 (52.4)
Hypomagnesemia	16 (76.2)	11 (52.4)	7 (33.3)
Rash	10 (47.6)	8 (38.1)	2 (9.5)
Acneiform dermatitis	9 (42.9)	8 (38.1)	2 (9.5)
Proteinuria	8 (38.1)	8 (38.1)	0
Increased blood alkaline phosphatase	4 (19.0)	4 (19.0)	0
Hyperthyroidism	4 (19.0)	4 (19.0)	0
Paronychia	3 (14.3)	3 (14.3)	0
Increased aspartate transferase	2 (9.5)	2 (9.5)	0
Increased alanine transferase	2 (9.5)	2 (9.5)	0
Hyperthyroidism	2 (9.5)	2 (9.5)	0
Hypothyroidism	2 (9.5)	2 (9.5)	0
Cough	2 (9.5)	2 (9.5)	0
Immune-mediated dermatitis	1 (4.8)	0	1 (4.8)
Atopic dermatitis	1 (4.8)	0	1 (4.8)
Hypokalemia	1 (4.8)	0	1 (4.8)
Increased creatine phosphokinase	1 (4.8)	0	1 (4.8)
Increased myoglobin levels	1 (4.8)	0	1 (4.8)
Skin infection	1 (4.8)	0	1 (4.8)

n, number.

SCT200 plus SCT-I10A cohort *vs.* SCT200 monotherapy cohort

We previously conducted a single-arm, phase I study to evaluate the efficacy and safety of SCT200 monotherapy as a third-line therapy for patients with mCRC. Twenty-five patients were included in the dose-expansion cohort and a clinical efficacy evaluation was performed. In this study we provided the survival and safety data of the aforementioned monotherapy cohort treated with a combination of SCT200 and SCT-I10A to provide a preliminary exploration of survival improvement after the addition of SCT-I10A. The baseline characteristics of the two cohorts are summarized in **Supplementary Table S3**.

The median OS (12.84 months *vs.* 20.16 months), median PFS (4.14 months *vs.* 5.22 months), and median DOR (2.87 months *vs.* 3.91 months) in the combination treatment cohort were not superior to the SCT200 monotherapy cohort (**Figure 2A–C**). Survival curves demonstrated no significant differences between patients with liver metastases and patients with lung metastases (**Figure 2D, E**). As mentioned above patients previously treated with cetuximab had a shorter median OS than patients without previous cetuximab treatment (**Figure 2F**). Surprisingly, when compared to the ORR [64.00% (16/25)] and DCR [92.00% (23/25)] of the SCT200 monotherapy cohort, the response rate of the combination group was slightly worse (ORR, 28.57%; DCR, 85.71%). In the SCT200 plus SCT-I10A cohort in this study, 11 (52.38%) patients experienced a reduction in tumor shrinkage from baseline, whereas in the previous monotherapy cohort, 22 (88.00%) patients showed tumor regression. Moreover, 6 responders (28.57%) in the combination cohort and 16 (64.00%) in the monotherapy cohort had tumor regression > 30% (**Figure 3**).



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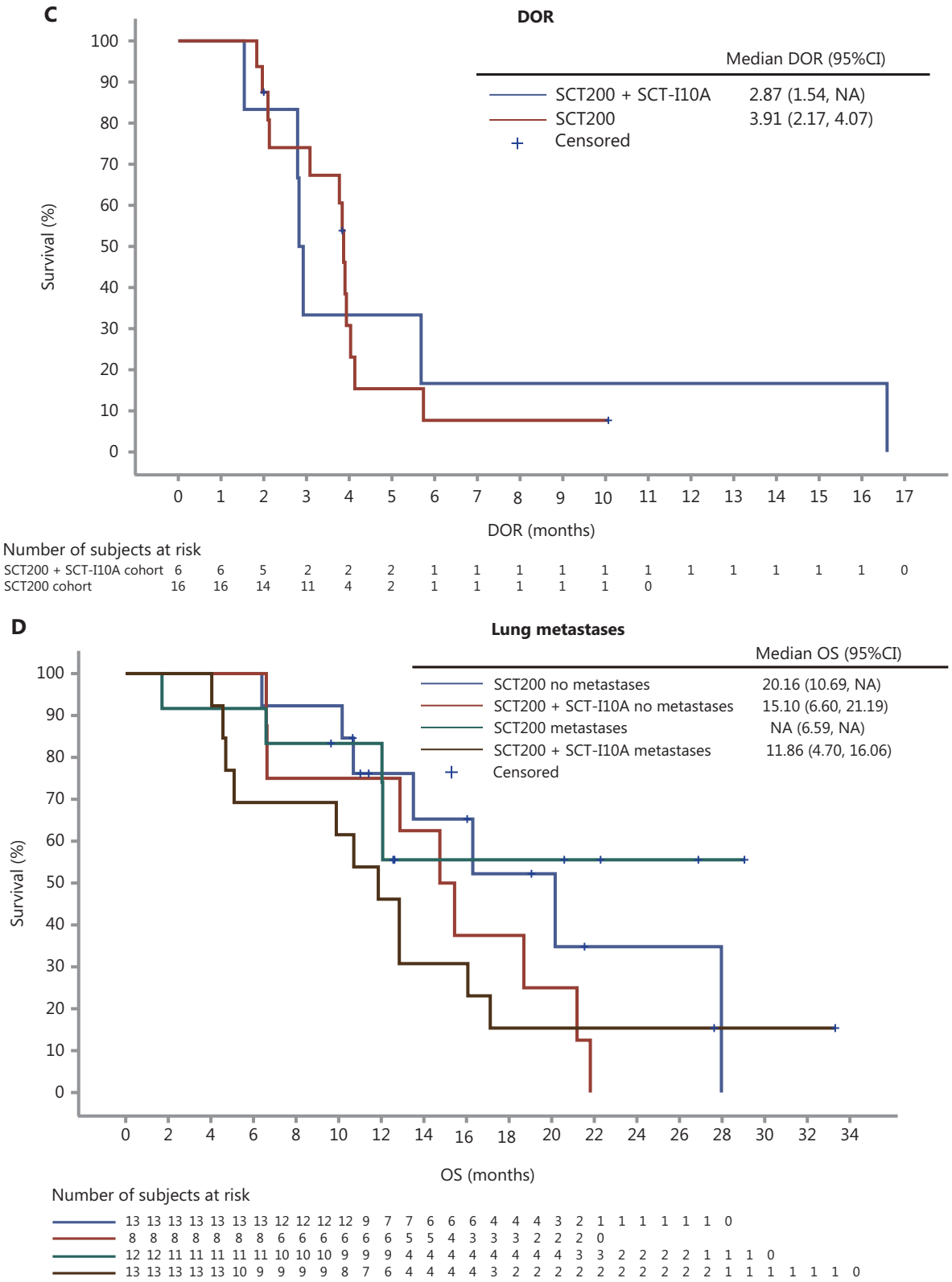

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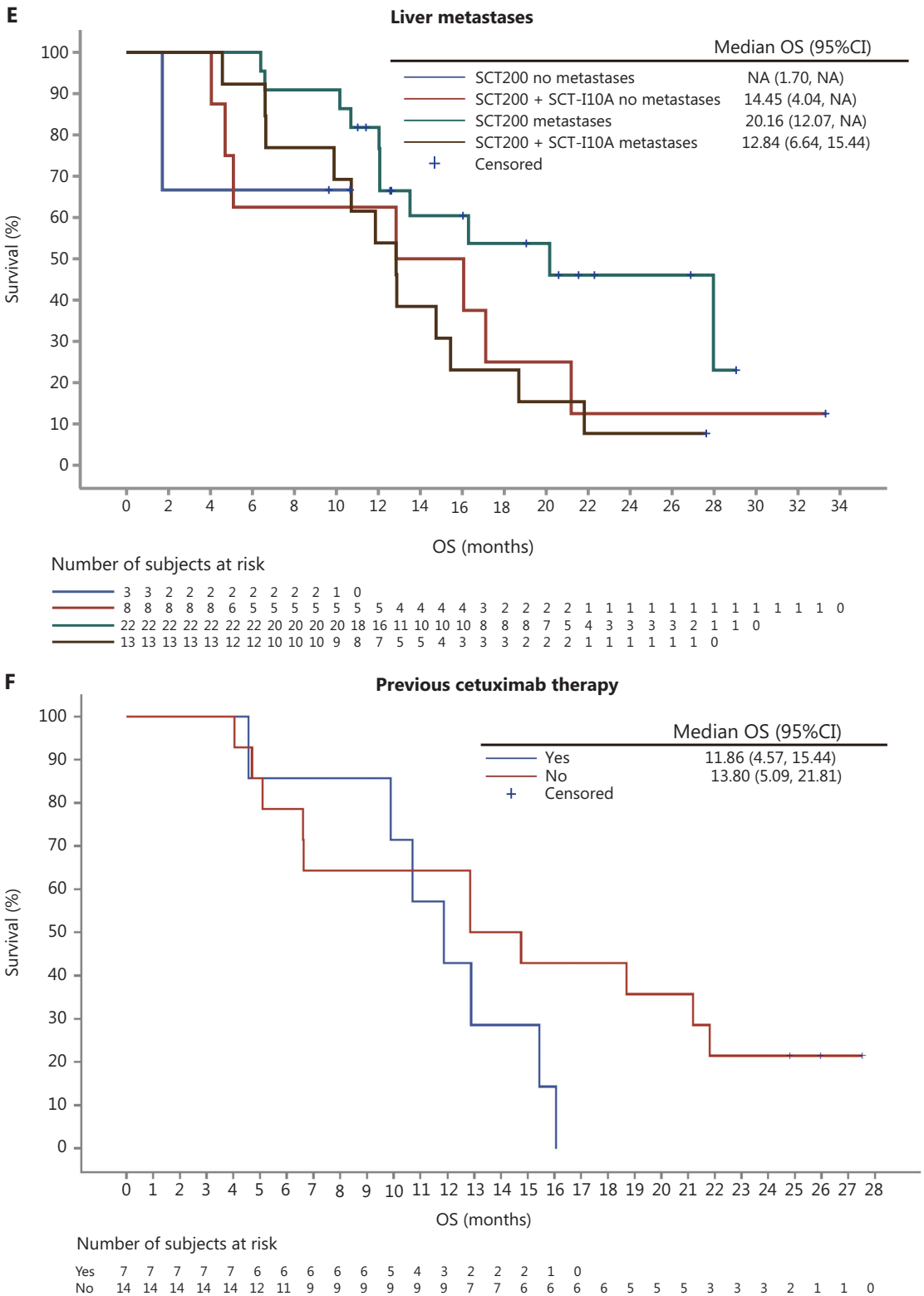
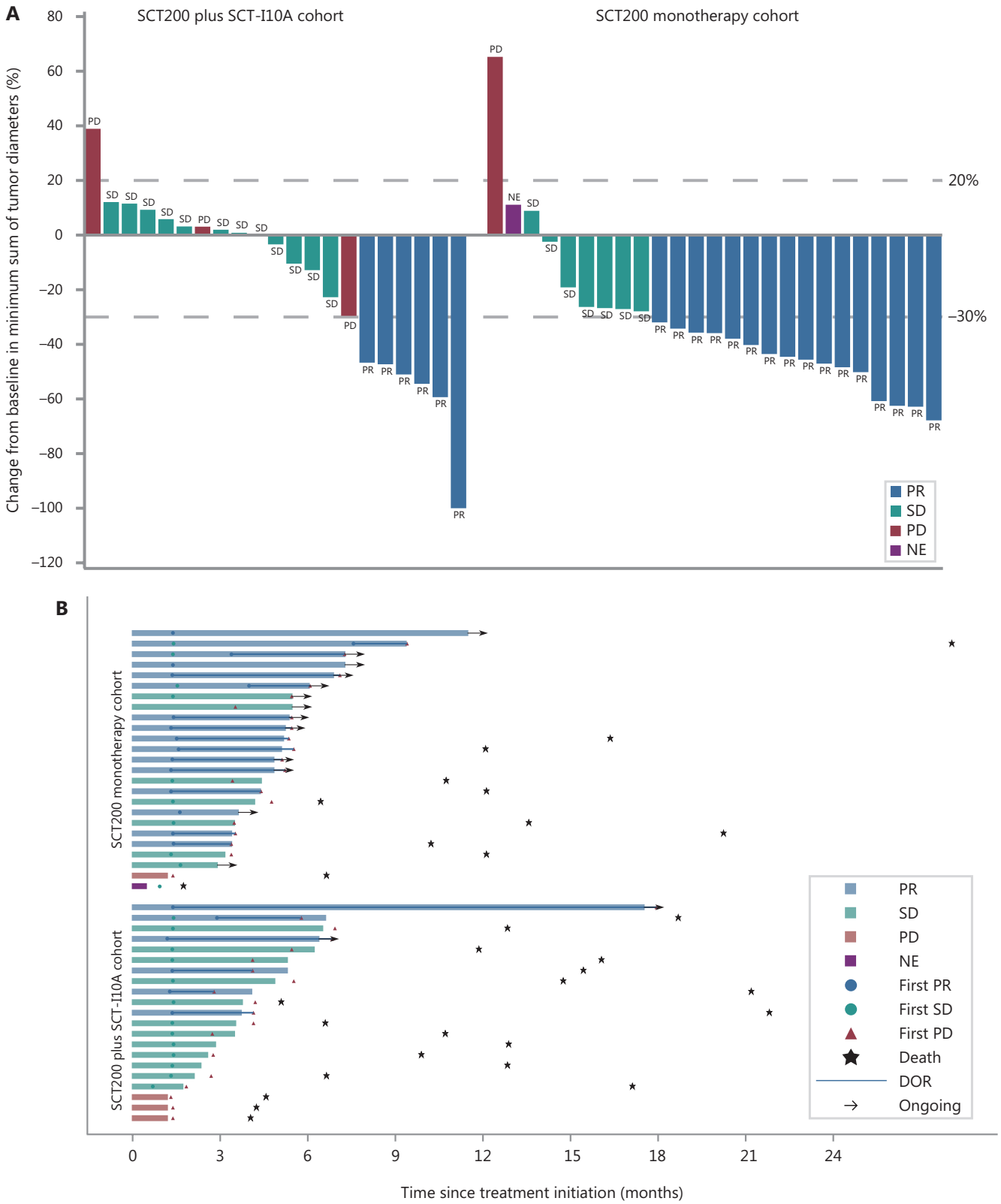


Figure 2 (A) Kaplan-Meier plots of overall survival (OS); (B) Kaplan-Meier plots of progression-free survival (PFS); (C) Kaplan-Meier plots of duration of response (DOR); (D) Kaplan-Meier plots of OS according to the presence of lung metastases; (E) Kaplan-Meier plots of OS according to the presence of liver metastases; (F) Kaplan-Meier plots of OS according to the presence of previous cetuximab therapy in SCT200 plus SCT-I10A cohort.



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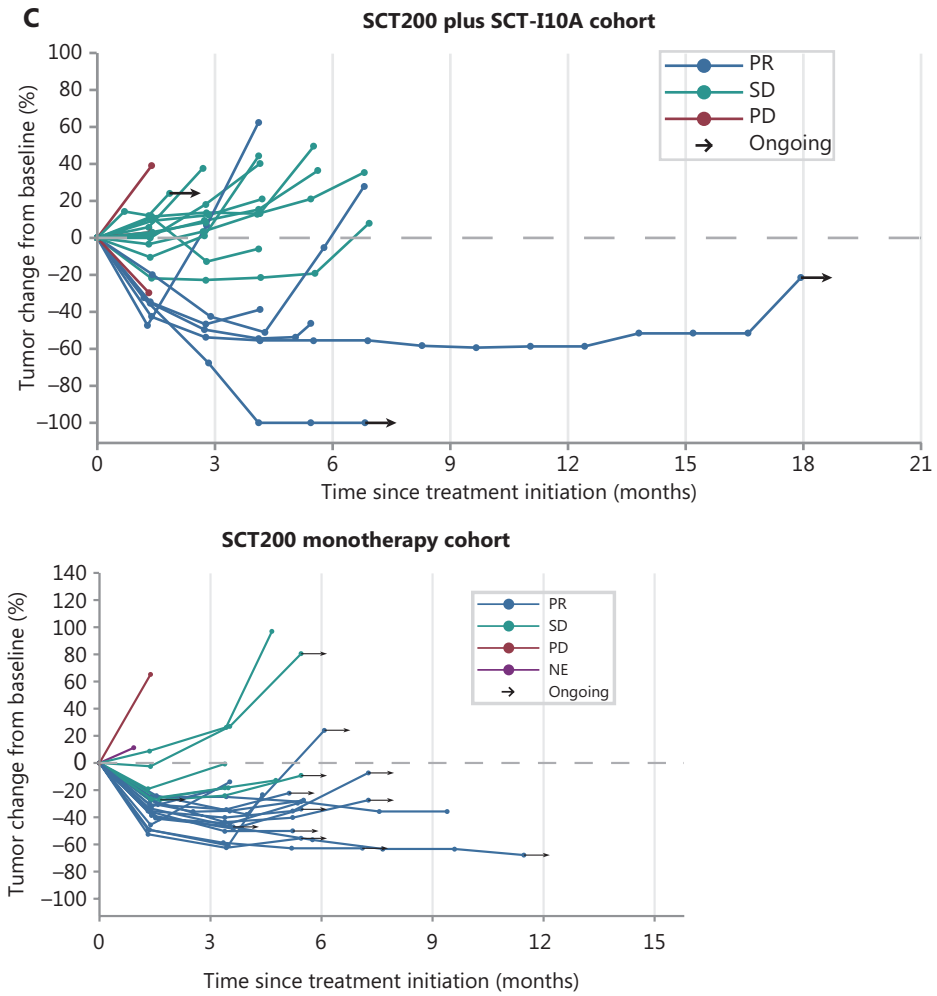

Figure 3 Records of responses and time during treatment (A), best percentage change in sum of diameters of target lesions from baseline according to RECIST (B), and longitudinal change in RECIST percentage from baseline (C) in the efficacy analysis set of SCT-I10A plus SCT200 cohort and SCT200 monotherapy cohort. (PR, partial response; SD, stable disease; PD, progressive disease; DOR, duration of response).

The safety analysis included 21 patients in the SCT200 plus SCT-I10A cohort and 25 in the SCT200 monotherapy cohort (**Supplementary Table S4**). The total incidence of TRAEs was similar between the two cohorts, with more grade 3 or 4 TRAEs observed in the combination treatment cohort. The incidence of hypophosphatemia and acneiform dermatitis was higher in the SCT200 monotherapy cohort, and the incidence of rashes and increased blood alkaline phosphatase levels were higher in the SCT200 plus SCT-I10A cohort.

Discussion

In this study we conducted an initial evaluation of the safety and clinical efficacy of combinational anti-EGFR mAb SCT200 with the anti-PD-1 inhibitor, SCT-I10A, in patients with mCRC who received two or more lines of systematic anti-cancer treatments. The results suggested that such combined treatment confers a favorable safety profile with clinical antitumor activity (ORR, 28.57%; median PFS, 4.14 months; median OS, 12.84 months), providing a promising third-line treatment option for patients with refractory mCRC.

Immunotherapy and targeted therapy have revolutionized the landscape of cancer treatment. During the last few decades, anti-VEGF- and anti-EGFR-based targeted therapy, and immune checkpoint inhibitor (ICI)-based immunotherapy have brought great survival benefits to patients with specific mCRC. Simultaneously, some small molecule inhibitor drugs are gradually being developed[35]. However, for patients that failed

previous treatment, clinical efficacy of the current third- or latter-line regimen (regorafenib, fruquintinib, and TAS-102) was limited, with a median OS of 6.4–9.3 months, a median PFS of 1.9–3.7 months, and an ORR of 1%–4.7%. Investigators are now exploring combined strategies of targeted, immune, and traditional chemotherapies for better disease control. Basic research has revealed that some targeted drugs can exert immunomodulatory effects, indicating that combining targeted and immune therapies may induce a synergistic effect[36]. A combination of anti-EGFR-targeted drugs with ICIs is one possible approach. The AVETUX study was a phase II study investigating avelumab and cetuximab combined with FOLFOX as first-line therapy for patients with RAS/BRAF wt mCRC[37]. The results showed that the AVETUX regimen was feasible, with a high response rate in patients with MSS, which mainly occurred within the first 8 weeks. In the field of later line settings, tislelizumab in combination with cetuximab and irinotecan showed encouraging clinical benefits (ORR, 36.4%; DCR, 78.8%) and a tolerable safety profile in patients with refractory RAS wt mCRC patients[38]. The AVETUXIRI study evaluated the efficacy and safety of avelumab combined with cetuximab and irinotecan in patients with refractory mCRC. The ORR was 30% and the DCR was 60% in patients with MSS and RAS/BRAF wt mCRC[39]. The CAVE study demonstrated that the combination of cetuximab with avelumab was a promising, well-tolerated rechallenge option for patients with RAS wt mCRC, with a median OS of 11.6 months, a median PFS of 3.6 months, and a DCR of 65%[32]. Panitumumab plus dual immunotherapy (ipilimumab and nivolumab) has also shown promising antitumor activity against RAS/BRAF wt, MSS, and refractory mCRC (median PFS, 5.7 months)[33]. Together with the results of our study, combining anti-EGFR targeted therapy with immunotherapy is a feasible and promising strategy for treating mCRC in a third-line setting.

Anti-angiogenesis-targeted drugs plus immunotherapy is another combination treatment for refractory mCRC. The REGONIVO trial demonstrated that regorafenib plus nivolumab has encouraging clinical benefits (ORR, 36%; median PFS, 7.9 months), with manageable safety in patients with mCRC receiving more than two lines of chemotherapy[40]. However, in a further phase II study, the ORR was only 27.1% in patients with MSS mCRC, which was far from satisfactory[41]. Another clinical study evaluating regorafenib plus nivolumab demonstrated similar results, with limited antitumor activity (ORR, 10.8%)[42]. The combination of regorafenib and dual immunotherapy (ipilimumab and nivolumab) achieved an ORR of 27.6%, a median OS of 20 months, and a median PFS of 4 months in patients with heavily pretreated MSS mCRC[43]. Currently, the efficacy of anti-angiogenic therapy combined with immunotherapy varies greatly in patients with mCRC.

Efficacy and cytotoxicity are major concerns when evaluating combined treatment regimens. A combined regimen that achieves an effect of one plus one or more with an acceptable safety profile determines the merit of clinical transformation. Because SCT200 monotherapy has produced a good antitumor response with favorable safety for patients with KRAS/NRAS/BRAF wt mCRC in a previous phase I trial, we also showed the survival and safety data of the dose-expansion cohort. It is worth noting that the efficacy of SCT200 plus SCT-I10A as third-line therapy for patients with RAS/BRAF wt mCRC was no better than SCT200 monotherapy. Differences in population characteristics between the two studies, as well as a relatively small sample size, may have contributed to this result. First, patients who had failed previous cetuximab treatment were included in this study, whereas in the previous SCT200 monotherapy study no patients had received front-line anti-EGFR therapy. Recent studies have demonstrated that prior use of anti-EGFR drugs significantly affect the efficacy of subsequent anti-EGFR mAb treatment. For instance, the ORR was approximately 7% in patients treated with cetuximab rechallenge treatment plus avelumab[32]. However, for patients who have not been treated with anti-EGFR mAbs, the response rate of combined anti-EGFR therapy with dual immunotherapy can reach 35%[33], indicating that previous anti-EGFR treatment may have influenced the efficacy of anti-EGFR mAbs as a later-line therapy. Severe TRAEs were observed more frequently in the SCT200 plus SCT-I10A cohort than the SCT200 monotherapy cohort. Combined drug cytotoxicity may hinder the expected synergistic benefits of combination therapy, particularly in patients who have undergone excessive line therapy. Advantageous population selection and optimization of drug combinations may be the future focus for clinical transformation. Finally, the combination arm only involved 21 patients and the dose-expansion cohort of the phase I trial involved 25 patients in the SCT200 monotherapy group. We did not perform a statistical analysis due to the differences in the enrolling population. Therefore, further head-to-head studies with larger sample sizes are needed to validate the efficacy of anti-EGFR mAbs combined with PD-1 inhibitors versus anti-EGFR monotherapy as a third-line treatment for mCRC.

Our study had some limitations. Based on the efficacy and safety of SCT200 monotherapy for mCRC confirmed in the phase Ib trial, we determined if SCT200 combined with SCT-I10A could achieve better efficacy. However, we found that the

efficacy and safety of combined therapy were not improved significantly during the experiment, so we did not continue enrolling patients. Therefore, considering the single-arm study design and small sample size, further large-scale cohorts are warranted for clinical transformation. The SCT200 plus SCT-I10A cohort and SCT200 monotherapy cohort are not from the same study. The survival data are only presented here and statistical comparison cannot be made considering the differences in the design and enrollment criteria. Therefore, we cannot make a conclusion about better treatment regimens. Relevant randomized controlled trials should be conducted to determine whether combined SCT200 with SCT-I10A can bring more survival benefits than SCT200 monotherapy. However, based on the data from this phase Ib clinical trial, SCT200 in combination with SCT-I10A as a third-line or subsequent treatment is a promising treatment for patients with mCRC. In the future, we will also conduct a phase III clinical trial to evaluate safety and efficacy of SCT200 plus SCT-I10A and chemotherapy in patients with mCRC.

Conclusions

Anti-EGFR antibody (SCT200) in combination with anti-PD-1 antibody (SCT-I10A) showed favorable clinical efficacy and an acceptable safety profile in patients with RAS and BRAF wt metastatic colorectal cancer in third- or subsequent line settings. Therefore, this combination may be a promising, active, and safe therapeutic option. Further head-to-head studies in a large population are needed to validate whether the efficacy and safety of combined anti-EGFR therapy with anti-PD-1 therapy are superior to those of anti-EGFR monotherapy in the third-line setting.

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Conflict of interest statement

Liangzhi Xie has potential stock option interests in the company. The other authors have no conflict of interest to declare.

Author contributions

Conceived and designed the analysis: Yi Ba.
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Contributed data or analysis tools: Yi Ba, Ming Bai, Yao Lu, Liangzhi Xie.
Performed the analysis: Yi Ba, Ming Bai, Yao Lu.
Wrote the paper: Yi Ba, Ming Bai, Yao Lu.

Data availability statement

The data generated in this study are available upon request from the corresponding author.

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