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ORIGINAL RESEARCH

Suvemcitug as second-line treatment of advanced or metastatic solid tumors and with FOLFIRI for pretreated metastatic colorectal cancer: phase Ia/Ib open label, dose-escalation trials

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Background: Suvemcitug (BD0801), a novel humanized rabbit monoclonal antibody against vascular endothelial growth factor, has demonstrated promising antitumor activities in preclinical studies.

Patients and methods: The phase Ia/b trials investigated the safety and tolerability and antitumor activities of suvemcitug for pretreated advanced solid tumors and in combination with FOLFIRI (leucovorin and fluorouracil plus irinotecan) in second-line treatment of metastatic colorectal cancer using a 3 + 3 dose-escalation design. Patients received escalating doses of suvemcitug (phase Ia: 2, 4, 5, 6, and 7.5 mg/kg; phase Ib: 1, 2, 3, 4, and 5 mg/kg plus FOLFIRI). The primary endpoint was safety and tolerability in both trials.

Results: All patients in the phase Ia trial had at least one adverse event (AE). Dose-limiting toxicities included grade 3 hyperbilirubinemia (one patient), hypertension and proteinuria (one patient), and proteinuria (one patient). The maximum tolerated dose was 5 mg/kg. The most common grade 3 and above AEs were proteinuria (9/25, 36%) and hypertension (8/25, 32%). Forty-eight patients (85.7%) in phase Ib had grade 3 and above AEs, including neutropenia (25/56, 44.6%), reduced leucocyte count (12/56, 21.4%), proteinuria (10/56, 17.9%), and elevated blood pressure (9/56, 16.1%). Only 1 patient in the phase Ia trial showed partial response, [objective response rate 4.0%, 95% confidence interval (CI) 0.1% to 20.4%] whereas 18/53 patients in the phase Ib trial exhibited partial response (objective response rate 34.0%, 95% CI 21.5% to 48.3%). The median progression-free survival was 7.2 months (95% CI 5.1-8.7 months).

Conclusions: Suvemcitug has an acceptable toxicity profile and exhibits antitumor activities in pretreated patients with advanced solid tumors or metastatic colorectal cancer.

Key words: advanced solid tumors, colorectal cancer, antiangiogenesis, suvemcitug, safety, antitumor activities

INTRODUCTION

Aberrant angiogenesis is a key driver of solid tumor growth and recurrence. Vascular endothelial growth factor (VEGF) and VEGF receptor (VEGFR) are essential for sustained cancer cell proliferation and growth. Antiangiogenesis agents, either as monotherapy or combination therapy, have demonstrated promising antitumor activities against lung cancer, ovarian cancer, and colorectal cancer (CRC).[1-3] Despite a myriad of currently available therapeutic options targeting oncoangiogenesis, novel antiangiogenic drugs are urgently needed to boost the armamentarium against advanced solid tumors.

CRC is occult in nature and mostly diagnosed at an advanced stage. Approximately 25% of CRC patients have metastases at the time of diagnosis and 40%-50% of newly diagnosed CRC patients with nodal infiltration and occult micrometastatic dissemination eventually develop metastases, with a 5-year overall survival (OS) <20%.[4] Systemic chemotherapy such as with FOLFOX (leucovorin and

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fluorouracil plus oxaliplatin) and FOLFIRI (leucovorin and fluorouracil plus irinotecan) is the primary treatment of metastatic CRC (mCRC) but fails to deliver a cure in most patients. Currently, FOLFOX or FOLFIRI combined with antiangiogenic agents like bevacizumab remains the standard of care (SOC) after failed first-line systemic therapy in mCRC.[5-7] Bevacizumab, ziv-aflibercept, and ramucirumab, however, each improve the OS of mCRC patients by merely 1-2 months versus placebo, necessitating the development of novel antiangiogenic agents.[8-10]

Patients who receive first-line bevacizumab-based therapy eventually develop progressive disease (PD) and require second-line therapy.[11] Bevacizumab, zif-aflibercept, and ramucirumab are approved by the US Food and Drug Administration as second-line antiangiogenic agents in combination with FOLFIRI for mCRC, but have not been compared head-to-head in randomized, controlled trials, with extension of OS no more than 2 months by each versus placebo.[8-10] Available evidence favors continuous antiangiogenesis with bevacizumab or another antiangiogenic monoclonal antibody in second- or later-line therapy. Prolonged use of existing antiangiogenic inhibitors drives the development of resistance, however, necessitating a search for new and more effective antiangiogenic drugs.[12]

Suvemcitug (BD0801), a novel humanized rabbit monoclonal IgG1 (κ) antibody against VEGF, selectively binds to and blocks VEGFA from binding to VEGFR1 and 2, thereby inhibiting its activities and preventing tumor angiogenesis and ultimately suppressing tumor growth and metastasis.[13] VEGFA is secreted in multiple forms, such as $VEGF_{121}$, $VEGF_{165}$, and $VEGF_{189}$, by alternative splicing.[14] Our unpublished and published preclinical studies show that although suvemcitug and bevacizumab have similar affinities to human $VEGF_{165}$, suvemcitug exhibits more potent functional activities than bevacizumab, including an apparently lower IC_{50} for inhibition of VEGF binding to VEGFR1 and VEGFR2, a lower IC_{50} for suppression of human umbilical vein endothelial cell (HUVEC) proliferation, and better activity in HUVEC wound healing assays, suggesting that suvemcitug may have greater antitumor potentials. Preclinical studies also showed that bevacizumab demonstrated synergistic antitumor activities with chemotherapy in CRC xenograft models or with immune checkpoint inhibitors in syngeneic tumor models including CRC.[13,15]

In the current study, we examined the safety and tolerability and antitumor activities of suvemcitug for patients with advanced solid tumors who had failed standard antitumor treatment or had no applicable standard treatment protocol and in combination with FOLFIRI in second-line treatment of mCRC patients.

MATERIAL AND METHODS

Study design and patients

The open label, phase Ia dose-escalation trial was conducted at two sites and enrolled patients with histologically or cytologically confirmed advanced or metastatic malignant solid tumors who had failed SOC or had no applicable standard treatment. The open label, phase Ib dose-escalation and expansion trial was conducted at multiple sites (Appendix 1) across China and enrolled patients with histologically or cytologically confirmed unresectable metastatic colorectal adenocarcinoma who had failed at least one first-line oxaliplatin-based chemotherapeutic regimen. Treatment failure referred to the development of PD during SOC or within 3 months of first-line chemotherapy, or recurrence or metastasis during or within 6 months of adjuvant chemotherapy, including oxaliplatin-based adjuvant chemotherapy. The main inclusion criteria for both trials were adult patients (18-74 years of age), at least one measurable lesion per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) score of 0 or 1, and adequate renal, hepatic, and bone marrow function. Additionally, patients should have received no chemotherapy within the preceding 4 weeks (6 weeks for mitomycin and nitrosourea). A wash-out period of at least four half-lives was required for biologics. The main exclusion criteria were symptomatic brain metastasis and prior treatment with anti-VEGF protein-based drugs. Detailed eligibility requirements for both trials are described in the trial protocols.

The trials are registered with Clinicaltrials.gov (NCT01847118 and NCT02453464).

Therapeutic interventions

Both trials used a 3 + 3 dose-escalation design with the intention of determining the maximum tolerated dose (MTD). Patients received escalating doses of suvemcitug (phase Ia: 2, 4, 5, 6, and 7.5 mg/kg; phase Ib: 1, 2, 3, 4, and 5 mg/kg; Shandong Simcere-MedGenn Bio-Pharmaceutical Co., Yantai, Shandong Province, China). Dose-limiting toxicities (DLTs) were determined based on the incidence and intensity of adverse events (AEs). Dose-escalation was based on the DLTs occurring on days 1-28 of the previous dose group. In the multiple dose stage (phase Ia), patients received suvemcitug every 2 weeks (Q2W) for totally three doses. In the phase Ib trial, patients received by intravenous infusion the FOLFIRI regimen [180 mg/m^2 irinotecan, 400 mg/m^2 leucovorin or 200 mg/m^2 levoleucovorin (equivalent to 400 mg/m^2 leucovorin), and 2400 mg/m^2 5-fluorouracil (5-FU) (400 mg/m^2 infused in the first 2-4 min followed by 1200 mg/m^2/d $\times$ 2 days)] on day 1 and suvemcitug on day 3 in the first cycle, and suvemcitug on day 1 followed by the FOLFIRI regimen in subsequent cycles. Each cycle lasted for 2 weeks. If no DLT was observed in the first 3 patients in a group at the end of cycle 2, or if only 1 out of 6 patients experienced DLT at the end of cycle 2, the group was expanded to include 8-12 patients.

Patients who had achieved at least stable disease (SD) after four infusions of suvemcitug and 4 weeks after the last dose of suvemcitug and had good tolerability were allowed to continue treatment as planned upon agreement by patients and investigator. Patients were treated until a confirmed complete response (CR), disease progression,

intolerable toxicities, receipt of a new antitumor therapy, or withdrawal from the study. Suvemcitug was discontinued upon occurrence of a DLT during the observation period for DLTs and dose reduction (2 to 1 mg and 1 to 0.5 mg) was allowed beyond the observation period.

Study endpoints

The primary endpoint was safety and tolerability in both trials. Safety was assessed using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0. Tumor response was evaluated per RECIST version 1.1 by investigators. CR and partial response (PR) had to be confirmed radiologically after at least 4 weeks. The secondary endpoints included objective response rate (ORR), disease control rate (DCR), and progression-free survival (PFS), which was calculated from the date of the initiation of treatment to the date of recorded disease progression, or death of any cause, whichever occurred earlier. OS (phase 1b) was calculated from the date of the start of treatment to the date of death of any cause.

Pharmacokinetics

Venous blood was collected via the cubital vein. Intensive and sparse sampling was implemented in the phase Ia trial and intensive sampling in the phase Ib trial. Serum suvemcitug concentrations were measured using a validated electrochemiluminescent immunoassay. The pharmacokinetic (PK) parameters after the first suvemcitug dose included the area under the concentration—time curve ($AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$), maximum concentration (C_{max}) and time to reach C_{max} (T_{max}), clearance (CL), apparent volume of distribution (V), mean residence time (MRT), and terminal elimination half-life ($t_{1/2}$). After multiple infusions, the PK parameters included $AUC_{0\text{-}t,}$ trough (Css_{min}) and peak concentration at steady state (Css_{max}), T_{max}, CL, V, MRT, and $t_{1/2}$. The PK parameters were calculated by the non-compartmental analysis model using WinNonLin® v6.4 (Certara USA Inc., Princeton, NJ). Dose linearity was determined by Power Model analysis.

Immunogenicity

Anti-drug antibodies (ADAs) were determined in the phase Ia trial using bridging enzyme-linked immunosorbent assay (ELISA). ADA-positive samples were further characterized for neutralizing antibody by validated competitive ELISA. The number and percentage of ADA-positive patients were recorded.

Statistical analysis

No sample size calculation based on statistical power was done. All statistical analyses were prespecified and followed the intention-to-treat principle and were conducted using SAS version 9.2 (SAS Institute Inc., Cary, NC). Efficacy analysis was based on the full analysis set (FAS), which included all patients who received at least one dose of suvemcitug and had a baseline assessment and at least one post-baseline efficacy assessment. ORR and DCR and their 95% confidence intervals (CIs) were estimated using the Clopper Pearson method. Missing endpoint relevant data were not imputed. The median PFS and OS were estimated, and the corresponding 95% CIs were calculated using the Brookmeyer and Crowley method and the survival curves for OS and PFS were estimated with the Kaplan—Meir method.

The safety set included all patients who received at least one dose of suvemcitug and had at least one safety evaluation, and was analyzed mainly using descriptive statistics. The DLT set included patients who completed the first two treatments in the dose-escalation phase and had been evaluated for DLT, or who had developed DLTs during evaluation. The PK set included patients who had received at least two cycles of chemotherapy with at least one measurable post-dose blood sample. All tests were two-tailed with a level of significance set at $\alpha \leq 0.05$.

RESULTS

Patient demographic and baseline characteristics and treatment

The study flowchart is shown in Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2023.101540. In the phase Ia trial, between 26 April 2013 and 15 December 2015, 35 patients with advanced malignant solid tumors were screened and 25 were eligible; 48% had CRC. They had a median age of 55.0 years (Q1-Q3, 49.0-58.0). All patients had metastases, most frequently to the lungs (64%), lymph nodes (60%), and the liver (60%). The patients were heavily pretreated with 88% of them having received at least two lines of prior chemotherapy (Table 1).

A total of 24 patients completed the dose-escalation stage, 10 patients completed the multiple dose stage, and 7 patients entered the extension phase. The median dose was 290 mg (range 130-640 mg) and the dose intensity reached 100% (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2023.101540).

In the phase Ib trial, between 2 December 2015 and 20 May 2019, 65 patients were screened, and 56 were eligible. All patients had metastasis, mostly to the liver (62.5%) or lungs (33.9%). All patients had received prior lines of chemotherapy, including 91.1% having received first-line chemotherapy and 8.9% having received second-line chemotherapy (Table 1). Patients received a median of 7.0 (Q1-Q3, 4.0-10.0) doses of suvemcitug and 47 patients (83.9%) completed 4 cycles of treatment, with 28.6% being exposed to at least 10 cycles of treatment. The mean total exposure was 1212.4 mg (Q1-Q3, 606.8-2025.0 mg) (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2023.101540). At the data cut-off (20 May 2019), no patients were receiving treatment. Fifty-six patients received at least 1 dose (median 6.0, Q1-Q3, 4.0-8.5 doses) of FOLFIRI, with 23.2% being exposed to at least 10 cycles of FOLFIRI. The mean total exposure was 1809.8 mg (Q1-Q3, 1183.8-2585.9 mg) for irinotecan, 4072.0 mg (Q1-Q3, 2552.0-5694.0 mg) for leucovorin, and 3978.0 mg (Q1-Q3, 2552.0-5694.0 mg) for 5-FU.

Table 1. Patient demographic and baseline characteristics

Characteristics	Ia	Ib
N	25	56
Median age, years (Q1-Q3)	55.0 (49.0-58.0)	56.5 (49.0～62.5)
Sex, *n* (%)		
Male	15 (60)	34 (60.7)
Female	10 (40)	22 (39.3)
ECOG, *n* (%)		
0	4 (16)	34 (60.7)
1	21 (84)	22 (39.3)
Type of solid tumors, *n* (%)		
Colorectal cancer	12 (48)	56 (100)
Breast cancer	4 (16)	0 (0.0)
Lung cancer	1 (4)	0 (0.0)
Gastric cancer	3 (12)	0 (0.0)
Ovarian cancer	1 (4)	0 (0.0)
Cervical cancer	1 (4)	0 (0.0)
Others	3 (12)	0 (0.0)
No. of metastatic foci, *n* (%)		
1	3 (12)	22 (39.3)
2	11 (44)	18 (32.1)
3	9 (36)	12 (21.4)
>3	2 (8)	4 (7.1)
Site of metastases, *n* (%)		
Lungs	16 (64)	19 (33.9)
Liver	13 (52)	35 (62.5)
Lymph nodes	15 (60)	27 (48.2)
Adrenal gland	1 (4)	0 (0.0)
Brain	2 (8)	0 (0.0)
Bones	6 (24)	1 (1.8)
Others	8 (32)	28 (50.0)
Surgery of the primary tumor, *n* (%)		
No	2 (8)	6 (10.1)
Yes	23 (92)	50 (89.3)
Surgery of metastatic tumors, *n* (%)		
No	17 (68)	45 (80.4)
Yes	8 (32)	11 (19.6)
Lines of prior chemotherapy, *n* (%)		
1	1 (4)	51 (92.1)
2	1 (4)	5 (8.9)
≥3	23 (92)	0 (0.0)
Radiotherapy, *n* (%)		
No	10 (4)	51 (91.1)
Yes	15 (60)	5 (8.9)
Comorbidities, *n* (%)		
No	3 (12)	15 (26.8)
Yes	22 (88)	41 (73.2)

ECOG, Eastern Cooperative Oncology Group.

Safety and tolerability

Among 25 patients eligible for DLT assessment in the phase Ia trial, 3 patients (12%) experienced DLTs, including grade 3 hyperbilirubinemia in 1 case and grade 3 hypertension and grade 3 proteinuria in 1 case receiving suvemcitug 7.5 mg/kg, and grade 3 proteinuria in 1 case receiving suvemcitug 6 mg/kg. The MTD was 5 mg/kg. Fifty-two patients were included in the DLT set in the phase Ib trial. DLTs occurred in two patients, fatigue in a patient receiving suvemcitug 2 mg/kg and proteinuria in a patient receiving suvemcitug 4 mg/kg. The MTD was not established. The recommended dose of suvemcitug was 2 mg/kg Q2W for subsequent clinical trials on suvemcitug plus FOLFIRI.

Twenty-five patients were included in the safety set in the phase Ia trial (Table 2). All patients had at least one AE. The most common grade 3 and above AEs were proteinuria (9/25, 36%) and hypertension (8/25, 32%). Treatment-related serious AEs (SAEs) occurred in two patients (8%), including probable gastrointestinal perforation and gastrointestinal hemorrhage in one case and grade 3 proteinuria in another. Treatment-related AEs led to discontinuation in nine patients (36%), including grade 3 proteinuria in four patients (16%), and grade 2 proteinuria worsening to grade 3, grade 3 hypertension, grade 2 hypertension worsening to grade 3, grade 2 hyperbilirubinemia and gastrointestinal hemorrhage each in one patient (4%).

Fifty-six patients were included in the safety set in the phase Ib trial (Table 2). All patients had at least one AE. A total of 48 patients (85.7%) had grade 3 and above AEs, including neutropenia (25/56, 44.6%), reduced leucocyte count (12/56, 21.4%), proteinuria (10/56, 17.9%), and elevated blood pressure (9/56, 16.1%). Additionally, 67.9% patients had grade 3 and above suvemcitug-related AEs. Some 18 patients (32.1%) developed SAEs and suvemcitug-related SAEs occurred in 10 patients (17.9%). One patient receiving suvemcitug 3 mg/kg died, which was probably treatment unrelated. A total of 41 patients (73.2%) experienced suvemcitug-related AEs causing dose reduction or treatment interruptions and 23 patients (41.1%) discontinued treatment due to suvemcitug-related AEs. Furthermore, AEs of special interest were reported in 50 patients (89.3%) (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2023.101540).

Antitumor activities

Tumor responses. In the phase Ia trial, 25 patients were included in the FAS. Twenty-four patients were assessable for efficacy at week 4. No patients attained CR and one patient receiving suvemcitug 7.5 mg/kg achieved PR. The ORR was 4.0% (95% CI 0.1% to 20.4%). Nineteen patients had SD and the DCR was 80.0% (95% CI 59.3% to 93.2%). Eleven patients were assessable for efficacy at week 12. No patients attained CR or PR. The ORR was 0% (95% CI 0.0% to 13.7%). Eight patients had SD and the DCR was 32.0% (95% CI 15.0% to 53.5%). Three patients had PD (Table 3 and Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2023.101540). At the study cut-off, the median PFS was 4.0 months (Q1-Q3, 2.1-4.1 months) (Figure 1A and B).

In the phase Ib trial, the FAS included 53 patients. No patients achieved CR whereas 34.0% of the patients attained PR. The ORR was 34.0% (95% CI 21.5% to 48.3%) (Table 3). A total of 51 patients (96.2%) achieved different extents of reduction in the target lesions, and 28 patients (52.8%) had >30% reduction in target lesion. Only two patients never achieved any shrinkage of the tumor (Figure 1C). In addition, 62.3% of the patients had SD; the DCR was 96.2% (95% CI 87.0% to 99.5%). Two patients developed PD, both in the 5 mg/kg group. The ORR was 54.7% (95% CI 40.5% to 68.4%) and the DCR was 96.2% (95% CI 87.0% to 99.5%) for unconfirmed responses. At the recommended dose of suvemcitug 2 mg/kg Q2W for subsequent clinical trials on suvemcitug plus FOLFIRI, the ORR

Table 2. Incidence of adverse events (AEs) that occurred in more than 10% of patients in either phase and grade 3 and above AEs

Phase Ia			Phase Ib		
Preferred terms	All grades	Grade 3 and above	Preferred terms	All grades	Grade 3 and above
Proteinuria	17 (68)	9 (36)	Reduced leucocyte count	41 (73.2)	12 (21.4)
Hypertension	17 (68)	8 (32)	Reduced neutrophil count	39 (69.6)	25 (44.6)
Positive occult urine test	9 (36)	0 (0)	Diarrhea	39 (69.6)	8 (14.3)
Fatigue	8 (32)	0 (0)	Vomiting	33 (58.9)	1 (1.8)
Rash	6 (24)	0 (0)	Fatigue	31 (55.4)	5 (8.9)
Reduced leucocyte count	6 (24)	0 (0)	Nausea	29 (51.8)	1 (1.8)
Reduced platelet count	5 (20)	0 (0)	Proteinuria	26 (46.4)	10 (17.9)
ECG abnormalities	5 (20)	0 (0)	Reduced platelet count	25 (44.6)	3 (5.4)
Elevated ALT	5 (20)	0 (0)	Elevated blood pressure	20 (35.7)	9 (16.1)
Peripheral edema	4 (16)	0 (0)	Abdominal pain	18 (32.1)	1 (1.8)
Headache	4 (16)	0 (0)	Nosebleed	17 (30.4)	—
Bradycardia	4 (16)	0 (0)	Reduced appetite	16 (28.6)	1 (1.8)
Hoarseness	4 (16)	0 (0)	Anemia	16 (28.6)	1 (1.8)
Elevated AST	4 (16)	0 (0)	Urinary protein	15 (26.8)	4 (7.1)
Reduced Hb	4 (16)	0 (0)	Fever	14 (25.0)	1 (1.8)
Cough	4 (16)	0 (0)	Reduced Hb	13 (23.2)	—
Nosebleed	3 (12)	0 (0)	Reduced lymphocyte count	13 (23.2)	1 (1.8)
Abdominal distension	3 (12)	0 (0)	Elevated TSH	13 (23.2)	—
Dizziness	3 (12)	0 (0)	Oral ulcer	13 (23.2)	—
Hand-foot syndrome	3 (12)	0 (0)	Oral mucositis	11 (19.6)	3 (5.4)
Itches	3 (12)	0 (0)	Elevated ALT	11 (19.6)	—
Elevated LDL	3 (12)	0 (0)	Diaphoresis	11 (19.6)	—
RBCs in urine	3 (12)	0 (0)	Elevated AST	10 (17.9)	—
Reduced neutrophil count	3 (12)	0 (0)	Hypertension	10 (17.9)	7 (12.5)
Hypoalbuminemia	3 (12)	0 (0)	Alopecia	10 (17.9)	—
—	—	—	Elevated triglyceride	9 (16.1)	1 (1.8)
—	—	—	Hypertriglyceridemia	9 (16.1)	2 (3.6)
—	—	—	Constipation	8 (14.3)	—
—	—	—	Hematuria	7 (12.5)	—
—	—	—	Dizziness	7 (12.50)	—
—	—	—	Hiccup	7 (12.50)	1 (1.8)
—	—	—	Reduced body weight	6 (10.7)	—
—	—	—	Elevated plasma glucose	6 (10.7)	—
—	—	—	Hypoalbuminemia	6 (10.71)	—
—	—	—	Intestinal obstruction	6 (10.71)	3 (5.4)
—	—	—	Insomnia	6 (10.71)	—

The treatment period was defined as the period after the first dose up to 28 days after the last dose.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; ECG, electrocardiogram; Hb, hemoglobin; LDL, low-density lipoprotein; RBC, red blood cell; TSH, thyroid stimulating hormone.

was 33.3% (95% CI 9.9% to 65.1%) and the DCR was 100.0% (95% CI 73.5% to 100.0%). In addition, suvemcitug 5 mg/kg Q2W plus FOLFIRI attained an ORR of 55.6% (95% CI 21.2% to 86.3%) (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2023.101540).

The median duration of follow up was 11.2 months. At the study cut-off, 28 PFS events had occurred in the FAS. The median PFS was 7.2 months (95% CI 5.1-8.7 months) (Figure 1D). The 6-month PFS rate reached 55.9% (95% CI 37.7% to 70.7%) and the 12-month PFS rate was 10.4% (95% CI 2.0% to 26.8%). In the FAS, 29 deaths were reported. The median OS was 15.4 months (95% CI 10.7 to 18.0 months) (Figure 1E). The 6- and 12-month OS rates were 91.2% (95% CI 78.1% to 96.6%) and 65.3% (95% CI 48.3% to 77.9%), respectively.

Table 3. Summary of best overall response per RECIST 1.1-FAS

	Phase Ia (*N* = 25)	Phase Ib (*N* = 53)	
		Confirmed	Unconfirmed
Best overall response, *n* (%)			
CR	0 (0)	0 (0)	0 (0)
PR	0 (0)	18 (34.0)	29 (54.7)
SD	8 (32.0)	33 (62.3)	22 (41.5)
PD	3 (12.0)	2 (3.8)	2 (3.8)
NE	14 (56)	0 (0)	0 (0)
ORR			
n% (95% CI)	0.0% (0.0% to 13.7%)	34.0% (21.5% to 48.3%)	54.7% (40.5% to 68.4%)
DCR			
n% (95% CI)	32.0% (15.0% to 53.5%)	96.2% (87.0% to 99.5%)	96.2% (87.0% to 99.5%)

ORR is defined as the proportion of subjects whose best overall response is confirmed CR or PR and DCR is defined as the proportion of patients who achieved CR, PR, or SD as their best overall response based on RECIST version 1.1.
CI, confidence interval; CR, complete response; DCR, disease control rate; FAS, full analysis set; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

PK

Figure 2A shows the plasma concentration—time profiles of suvemcitug in the phase Ia trial. C_{max} was linearly

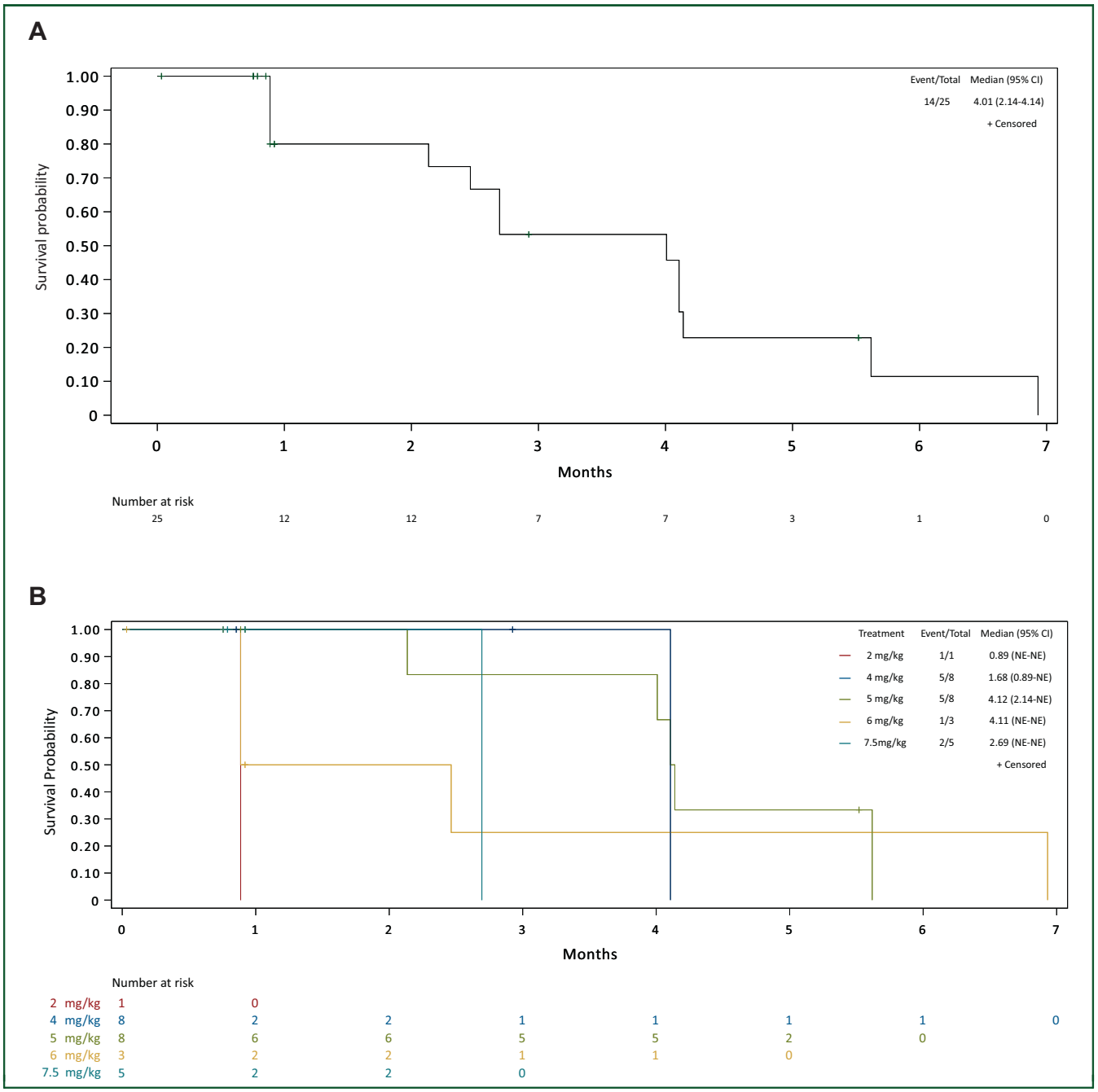


Figure 1. The Kaplan–Meier curves of (A) progression-free survival (PFS) of the full analysis set and (B) each dose group in the phase Ia trial. (C) Waterfall plots of the best percentage changes for the sum of target lesion diameters after treatment are shown for individual patients with best objective response per RECIST version 1.1. Investigator-confirmed responses are included. The dotted line indicates a 30% reduction in the target lesion size. Each bar in the *x*-axis represents one patient in the full analysis set. The Kaplan–Meier curves of PFS (D) and (E) overall survival (OS) of the full analysis set in the phase Ib trial.
CI, confidence interval; NE, not evaluable.

associated with doses administered and the *in vivo* exposure ($AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$) showed a dose-dependent increase. The C_{max} (40.70 μg/ml) was reached 3.5 h after a single infusion of suvemcitug 2 mg/kg, with an $AUC_{0\text{-}t}$ of 4633.49 μg·h/ml (Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2023.101540). The mean C_{max} reached 175.70 ± 84.37, 195.72 ± 48.38, 208.72 ± 83.77, and 235.08 ± 125.67 μg/ml after a single infusion of suvemcitug 4, 5, 6, and 7.5 mg/kg, respectively, with a corresponding $AUC_{0\text{-}t}$ of 23 757.30 ± 9122.58, 29 904.67 ± 11 005.50, 39 259.77 ± 13 545.22, and 47 648.54 ± 17 441.87 μg·h/ml. The $t_{1/2}$ of suvemcitug also increased dose dependently. Meanwhile, CL remained steady with suvemcitug 4-7.5 mg/kg. The trough and peak plasma concentrations of suvemcitug steadily increased after multiple infusions until week 8 and declined thereafter. The mean C_{max} increased to 108.44 ± 13.48, 138.24 ± 25.22, 133.53 ± 29.17, and 188.47 ± 63.65 μg/ml after a single infusion of suvemcitug 4, 5, 6, and 7.5 mg/kg, respectively, with a corresponding $AUC_{0\text{-}t}$ of 16 251.75 ± 2446.18, 20

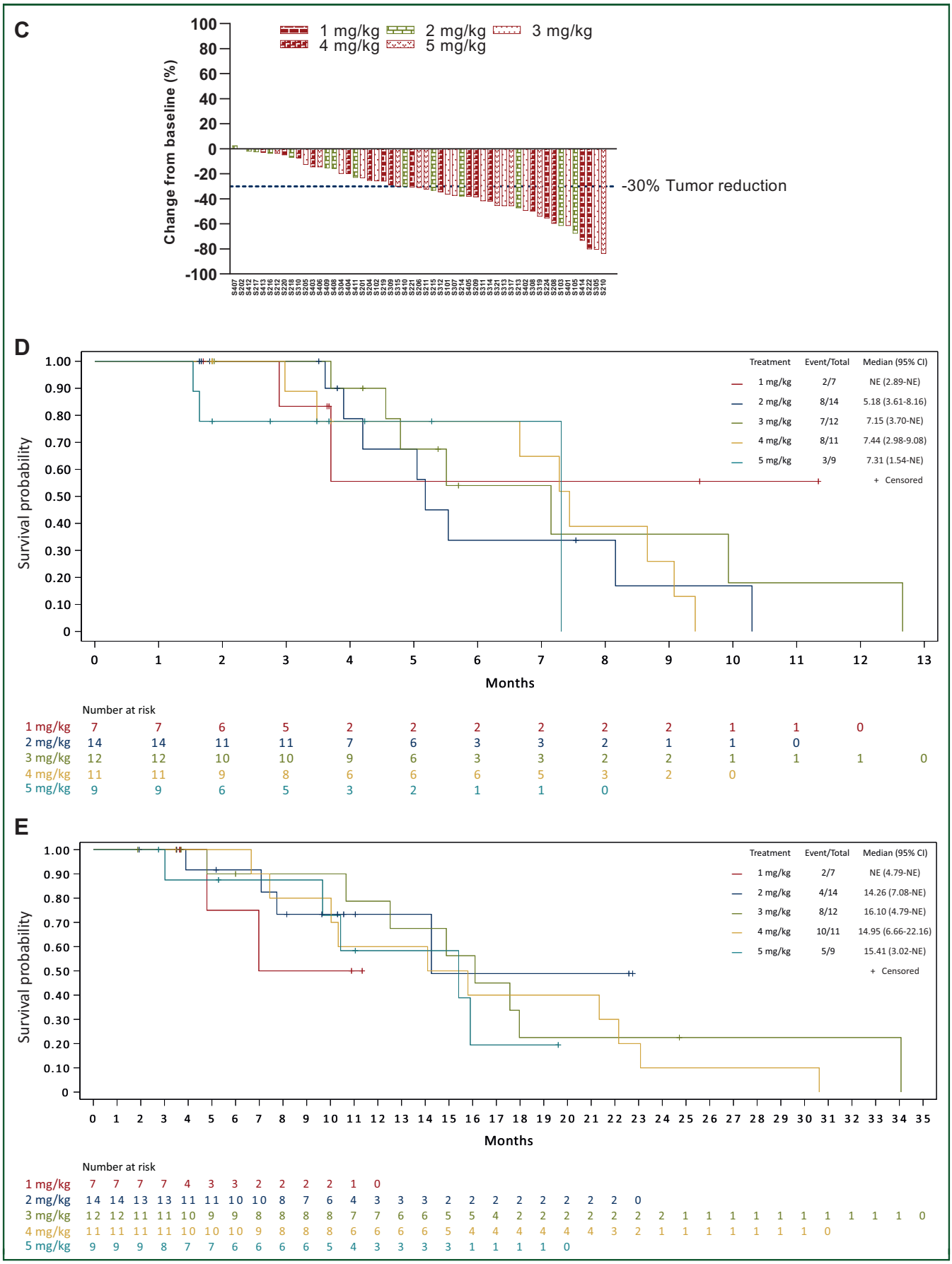


Figure 1. Continued.

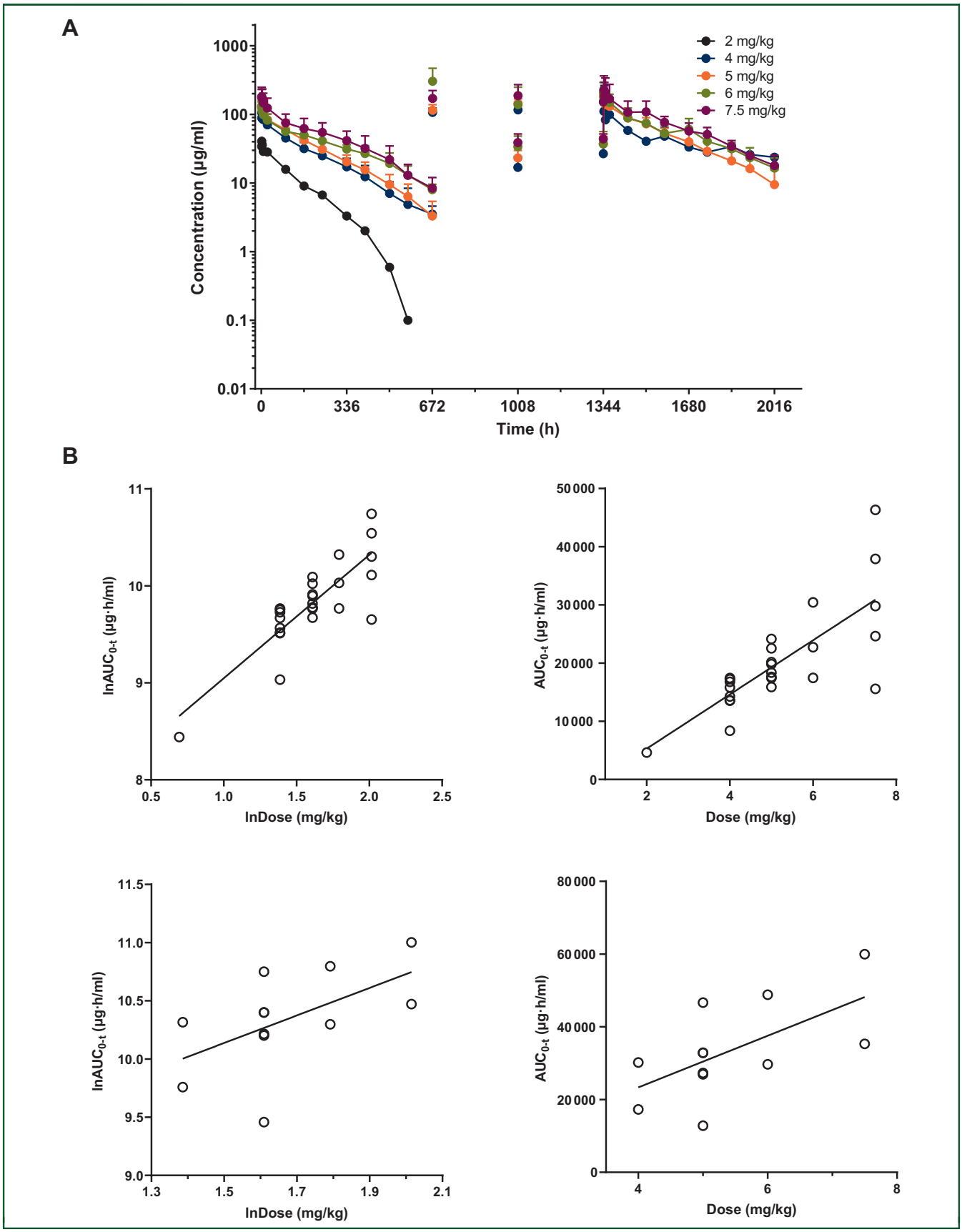


Figure 2. **(A) The plasma concentration—time profiles of suvemcitug following the first infusion of 2, 4, 5, 6, and 7.5 mg/kg suvemcitug and the second, third, and fourth infusion of 4, 5, 6, and 7.5 mg/kg suvemcitug in patients with solid tumors. (B) Power Model analysis shows a linear growth in C_{max} of suvemcitug after the first (top panel) and second infusion (bottom).**

940.2 ± 3465.94, 26 566.84 ± 7960.49, and 33 570.57 ± 12 085.28 μg·h/ml. The accumulation ratio was 1.4 ± 0.5, 1.6 ± 0.6, 1.5 ± 0.2, and 1.9 ± 0.5 after multiple infusions of suvemcitug 4, 5, 6, and 7.5 mg/kg, respectively. Power Model analysis showed a linear growth in C_{max} (first dose: slope estimate: 1.27 ± 0.17, 90% CI 0.91-1.63 and second dose: slope estimate: 1.18 ± 0.55, 90% CI −0.04 to 2.41) for suvemcitug between 4 and 7.5 mg/kg (Figure 2B).

The PK results of the phase Ib trial are shown in Supplementary Table S5 and Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2023.101540.

Immunogenicity

In the phase 1a trial, the incidence of ADA was 12% (3/25) and no neutralizing antibodies were detected. ADA was detected before the first infusion in two patients, with one receiving suvemcitug 5 mg/kg and the other receiving 6 mg/kg (Supplementary Table S6, available at https://doi.org/10.1016/j.esmoop.2023.101540).

DISCUSSION

The paradigm of treatment of mCRC has changed considerably in the previous decade.[16] The advent of antiangiogenic agents including bevacizumab and aflibercept has boosted the therapeutic armamentarium against this disease, leading to remarkable improvement in survival outlook for many patients in this population. Both suvemcitug and bevacizumab selectively bind to and block VEGFA from binding to VEGFR1 and VEGFR2, whereas ramucirumab targets the extracellular domain of VEGFR2.[17] These antiangiogenic drugs have exhibited similar efficacy and toxicity profiles, however, and there is an urgent need for defining the role of different antiangiogenic agents in the second-line setting and identifying effective biomarkers predictive of response to antiangiogenic therapy in order to provide guidance for physicians in selecting the optimal option for a given patient.

The current dose-escalation/dose-expansion trials evaluated suvemcitug in patients with advanced solid tumors who had failed or had no applicable SOC, and in combination with doublet FOLFIRI in second-line treatment of mCRC patients. The MTD was 5 mg/kg Q2W for suvemcitug monotherapy of advanced solid tumors and was not established for suvemcitug plus FOLFIRI for mCRC. The recommended dose of suvemcitug was 2 mg/kg Q2W for subsequent clinical trials on suvemcitug plus FOLFIRI for mCRC. DLTs included hyperbilirubinemia, hypertension, proteinuria, and fatigue.

Suvemcitug had an acceptable safety profile, with no new safety concerns in the study. The most common grade 3 and above AEs were proteinuria (36%) and hypertension (32%) (phase Ia) and neutropenia (44.6%) and reduced leucocyte count (21.4%) and proteinuria (17.9%) (phase Ib). Meanwhile, no grade 3 or higher neutropenia occurred in the phase Ia trial. Neutropenia is the most common AE associated with chemotherapy and a determinant of treatment continuation and outcome.[18] FOLFIRI plus bevacizumab was associated with a high incidence of grade 3 or higher neutropenia (45%) in patients with mCRC.[19] In our phase Ia/Ib trials, no febrile neutropenia was reported. Hypertension occurred in 12.5% patients in the phase Ib trial. Hemorrhage, thromboembolism, proteinuria, and hypertension are known AEs associated with bevacizumab treatment, which may be related to inhibition of VEGF signaling.[20] Hypertension occurs as an off-target effect of kinase inhibitor therapies.[21] With an IC_{50} of 21.0 and 275.4 ng/ml, VEGFR1 and VEGFR2 inhibition by suvemcitug might account for the lower rates of hypertension in our trials versus bevacizumab, with an IC_{50} of 6760 and 1451 ng/ml for VEGFR1 and VEGFR2, respectively.[13] Thromboembolism also occurred in neither trial. The AEs, including DLTs, were effectively controlled with standard treatments. VEGF inhibition may cause local tissue hypoxia and impair wound healing and could increase the risk of gastrointestinal perforation. The incidence of gastrointestinal perforation was reported in 1.5% patients receiving bevacizumab plus fluorouracil, and leucovorin.[22] One patient in the phase Ia trial developed grade 2 gastrointestinal perforation, leading to treatment discontinuation. Overall, the safety profile of suvemcitug in our patients is consistent with that of bevacizumab.

Suvemcitug monotherapy had an ORR of 4.0% and a DCR of 80.0% at 4 weeks and 32.0% at 12 weeks, indicating that suvemcitug monotherapy had antitumor activities against advanced solid tumors failing standard antitumor treatment or with no applicable standard treatment protocol. Notably, suvemcitug plus FOLFIRI as second-line treatment of mCRC attained an ORR of 34.0% and achieved a remarkable DCR of 96.2%, demonstrating antitumor activities of antiangiogenic therapy plus chemotherapy, when compared with an ORR of 5% to 21% for second-line bevacizumab plus chemotherapy, 19.8% for second-line aflibercept plus FOLFIRI, and 13.4% for second-line ramucirumab plus FOLFIRI for mCRC.[10,23,24] Moreover, suvemcitug 5 mg/kg Q2W plus FOLFIRI attained an ORR of 55.6%, which is apparently higher than that (33.3%) with suvemcitug 2 mg/kg Q2W, the recommended dose of suvemcitug for subsequent clinical trials on suvemcitug plus FOLFIRI. This better efficacy is supported by the PK results of suvemcitug plus FOLFIRI, with a greater $C_{max,}$ and $AUC_{(0\text{-}inf)}$ with suvemcitug 5 mg/kg Q2W than suvemcitug 2 mg/kg Q2W. Better disease control was seen with single agent suvemcitug, with a DCR of 0.0% with suvemcitug 2 mg/kg versus 100% with suvemcitug 5 mg/kg, the MTD in the phase Ia trial.

Suvemcitug plus FOLFIRI achieved a median PFS of 7.2 months, which is comparable to that (5.7-6.8 months) achieved with second-line chemotherapy plus bevacizumab, bevacizumab or ramucirumab.[8,10,23,24] Suvemcitug plus FOLFIRI also attained a median OS of 15.4 months, with a 12-month OS of 65.3%. The OS is comparable to 15.0 months with second-line aflibercept plus FOLFIRI[8] but longer than 12.9 months with second-line FOLFOX plus bevacizumab for pretreated mCRC.[8,25]

PK analysis showed a dose-dependent increase in plasma suvemcitug concentrations at single doses between 2 and

7.5 mg/kg, with a linear growth in C_{max} between suvemcitug 4 and 7.5 mg/kg, and between 1 and 5 mg/kg in combination treatment with FOLFIRI. The accumulation ratio varied between 1.4 and 1.9 after multiple infusions of suvemcitug as monotherapy at doses from 4 to 7.5 mg/kg and between 0.84 and 1.50 after multiple infusions of 1 to 5 mg/kg suvemcitug plus FOLFIRI. The lack of apparent accumulation of suvemcitug as monotherapy or in combination with chemotherapy may explain the overall acceptable safety profile of suvemcitug in the phase Ia/b trials. Neutralizing ADAs could hamper the effectiveness of treatment. Twelve percent of the patients in the phase Ia trial were positive for ADA; however, no neutralizing antibodies were detected.

The current trials had several limitations. The study did not include mCRC patients who had been previously treated with anti-VEGF protein-based drugs including bevacizumab. When the current study was started, bevacizumab had been just recommended as part of SOC in the first-line treatment of mCRC in the 2015 treatment guidelines by the National Health Commission of the People's Republic of China.[26] Access to bevacizumab was suboptimal, however, with treatment costs acting as the main barrier. Furthermore, benefit of cross-line treatment with bevacizumab had not been established before the initiation of our phase 1b trial. Additionally, the number of subjects was small and there was lack of a comparator treatment arm in both trials, and the patient population was heterogeneous in the phase Ia trial, which are expected for early phase clinical trials. Furthermore, tumor response was evaluated per investigators rather than by centralized review. Moreover, biomarkers were not studied which could guide molecularly stratified treatment of CRC patients.

Conclusions

In summary, suvemcitug demonstrated an acceptable risk—benefit profile given the safety results and tumor responses in patients with advanced solid tumors and patients with mCRC. Our findings suggest that suvemcitug could benefit patients with advanced solid tumors or mCRC who have failed first-line therapy. Additional investigation of the safety and efficacy of suvemcitug as monotherapy or in combination with chemotherapy or immunotherapy is warranted.

FUNDING

None declared.

DISCLOSURE

Jiangsu Simcere Pharmaceuticals Co. Ltd., the sponsor of this trial, provided all trial costs, including investigational drugs, laboratory tests, and associated operational cost. WS, LL, YW, LS, XF, and JZ are full-time employees of Shandong Simcere Bio-Pharmaceutical Co., Ltd. Both Jiangsu Simcere Pharmaceuticals Co. Ltd. and Shandong Simcere Bio-Pharmaceutical Co., Ltd are subsidiaries of Simcere Pharmaceuticals Co., Ltd. All other authors have declared no conflicts of interest.

REFERENCES

1. Mody K, Baldeo C, Bekaii-Saab T. Antiangiogenic therapy in colorectal cancer. *Cancer J*. 2018;24:165-170.
2. Ren S, Xiong X, You H, Shen J, Zhou P. The combination of immune checkpoint blockade and angiogenesis inhibitors in the treatment of advanced non-small cell lung cancer. *Front Immunol*. 2021;12:689132.
3. Chambers A, Kundranda M, Rao S, Mahmoud F, Niu J. Anti-angiogenesis revisited: combination with immunotherapy in solid tumors. *Curr Oncol Rep*. 2021;23:100.
4. National Cancer Institute Surveillance, Epidemiology, and End Results Program. Cancer stat facts: colorectal cancer. Available at https://seer.cancer.gov/statfacts/html/colorect.html. Accessed January 28, 2022.
5. Biller LH, Schrag D. Diagnosis and treatment of metastatic colorectal cancer: a review. *J Am Med Assoc*. 2021;325:669-685.
6. Van Cutsem E, Cervantes A, Adam R, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann Oncol*. 2016;27:1386-1422.
7. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: colon cancer, version 3; 2019. Available at https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed October 3, 2019.
8. Van Cutsem E, Tabernero J, Lakomy R, et al. Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. *J Clin Oncol*. 2012;30:3499-3506.
9. Folprecht G, Pericay C, Saunders MP, et al. Oxaliplatin and 5-FU/folinic acid (modified FOLFOX6) with or without aflibercept in first-line treatment of patients with metastatic colorectal cancer: the AFFIRM study. *Ann Oncol*. 2016;27:1273-1279.
10. Tabernero J, Yoshino T, Cohn AL, et al. Ramucirumab versus placebo in combination with second-line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): a randomised, double-blind, multicentre, phase 3 study. *Lancet Oncol*. 2015;16:499-508.
11. Jang HJ, Kim BJ, Kim JH, Kim HS. The addition of bevacizumab in the first-line treatment for metastatic colorectal cancer: an updated meta-analysis of randomized trials. *Oncotarget*. 2017;8:73009-73016.
12. Itatani Y, Kawada K, Yamamoto T, Sakai Y. Resistance to anti-angiogenic therapy in cancer-alterations to anti-VEGF pathway. *Int J Mol Sci*. 2018;19:1232.
13. Xue L, Gao X, Zhang H, et al. Antiangiogenic antibody BD0801 combined with immune checkpoint inhibitors achieves synergistic antitumor activity and affects the tumor microenvironment. *BMC Cancer*. 2021;21:1134.
14. Holmes DI, Zachary I. The vascular endothelial growth factor (VEGF) family: angiogenic factors in health and disease. *Genome Biol*. 2005;6:209.
15. Zhang Y, Sun M, Huang G, et al. Maintenance of antiangiogenic and antitumor effects by orally active low-dose capecitabine for long-term cancer therapy. *Proc Natl Acad Sci U S A*. 2017;114:E5226-E5235.
16. De Falco V, Napolitano S, Roselló S, et al. How we treat metastatic colorectal cancer. *ESMO Open*. 2020;4:e000813.
17. Jimenez X, Lu D, Brennan L, et al. A recombinant, fully human, bispecific antibody neutralizes the biological activities mediated by both vascular endothelial growth factor receptors 2 and 3. *Mol Cancer Ther*. 2005;4:427-434.
18. Yoshida Y, Hoshino S, Aisu N, et al. Can grade 2 neutropenia predict the risk of grade 3 neutropenia in metastatic colorectal cancer patients treated with chemotherapy? *Support Care Cancer*. 2015;23:1623-1627.
19. Yamazaki K, Nagase M, Tamagawa H, et al. Randomized phase III study of bevacizumab plus FOLFIRI and bevacizumab plus mFOLFOX6 as first-line treatment for patients with metastatic colorectal cancer (WJOG4407G). *Ann Oncol*. 2016;27:1539-1546.
20. Shui L, Wu YS, Lin H, Shui P, Sun Q, Chen X. Triplet chemotherapy (FOLFOXIRI) plus bevacizumab versus doublet chemotherapy (FOLFOX/

FOLFIRI) plus bevacizumab in conversion therapy for metastatic colorectal cancer: a meta-analysis. *Cell Physiol Biochem*. 2018;48:1870-1881.
21. Robinson ES, Khankin EV, Karumanchi SA, Humphreys BD. Hypertension induced by vascular endothelial growth factor signaling pathway inhibition: mechanisms and potential use as a biomarker. *Semin Nephrol*. 2010;30:591-601.
22. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med*. 2004;350:2335-2342.
23. Bennouna J, Sastre J, Arnold D, et al. Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial. *Lancet Oncol*. 2013;14:29-37.
24. Masi G, Salvatore L, Boni L, et al. Continuation or reintroduction of bevacizumab beyond progression to first-line therapy in metastatic colorectal cancer: final results of the randomized BEBYP trial. *Ann Oncol*. 2015;26:724-730.
25. Giantonio BJ, Catalano PJ, Meropol NJ, et al. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. *J Clin Oncol*. 2007;25:1539-1544.
26. National Health Commission of the People's Republic of China. Available at https://www.nhc.gov.cn/ewebeditor/uploadfile/2015/10/20151022092655999.doc. Accessed March 10, 2023.

APPENDIX 1

List of participating centers
Phase 1a trial:
Fudan University Shanghai Cancer Hospital
The First Hospital of Jilin University

Phase 1b trial:
Fudan University Shanghai Cancer Hospital
The first Affiliated Hospital of Medical College of Zhejiang University
The First Hospital of Jilin University
Harbin Medical University Cancer Hospital