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Results of a phase 1/2 study of sacituzumab tirumotecan in patients with unresectable locally advanced or metastatic solid tumors refractory to standard therapies

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Abstract

Background Sacituzumab tirumotecan (sac-TMT) is an antibody–drug conjugate composed of an anti-TROP2 monoclonal antibody coupled to a cytotoxic belotecan-derived topoisomerase I inhibitor (KL610023) via a novel linker. We report results from the phase 1 dose-escalation cohorts in advanced solid tumors and phase 2 expansion cohorts for metastatic triple-negative breast cancer (TNBC) from the first-in-human MK-2870-001 (KL264-01) study (NCT04152499).

Methods Patients had unresectable locally advanced/metastatic solid tumors refractory to standard therapies. In the phase 1 dose-escalation cohorts, patients had unresectable locally advanced/metastatic solid tumors refractory to standard therapies. Sac-TMT was administered by intravenous administration every 2 weeks at 2 to 12 mg/kg. In phase 2, patients with TNBC and HR+/HER2− breast cancer received sac-TMT per recommended doses for expansion (RDEs) identified in phase 1. Primary objectives were determining maximum tolerated dose (MTD) of sac-TMT and establishing RDEs (phase 1) and determining ORR per RECIST v1.1 by investigator assessment (phase 2). Adverse events were assessed per NCI-CTCAE version 5.0.

Results Thirty patients were enrolled in phase 1 and received sac-TMT 2 mg/kg ($n=4$), 4 mg/kg ($n=7$), 5 mg/kg ($n=7$), 5.5 mg/kg ($n=5$), and 6 mg/kg ($n=7$). Five patients had dose-limiting toxicities: grade 3 stomatitis at 4, 5.5, and 6 mg/kg; grade 3 rash at 5 mg/kg; and grade 3 urticaria at 6 mg/kg. MTD was 5.5 mg/kg and RDEs were 4 and 5 mg/kg. In the phase

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2 dose expansion, ORR (95% CI) was 34.8% (16.4%, 57.3%) in the 4-mg/kg group ($n=23$) and 38.9% (23.1%, 56.5%) in the 5-mg/kg group ($n=36$) for TNBC. ORR (95% CI) was 31.7% (18.1%, 48.1%) for HR+/HER2− breast cancer ($n=41$).

Conclusions Sac-TMT demonstrated manageable safety profile in patients with unresectable locally advanced/metastatic solid tumors and promising antitumor activity in metastatic TNBC and HR+/HER2 − breast cancer. Sac-TMT is being investigated in phase 3 studies.

Trial registration ClinicalTrials.gov, NCT04152499.

Keywords Sac-TMT, Antibody–drug conjugate, Triple-negative breast cancer, HR+/HER2− breast cancer

Introduction

Immunotherapy has been an integral part of the standard of care for many solid tumors, including metastatic triple-negative breast cancer (TNBC) [1, 2]. However, a substantial proportion of patients with metastatic TNBC or hormone receptor–positive (HR+)/human epidermal growth factor receptor 2–negative (HER2–) breast cancer will not respond to immunotherapy (ie, primary resistance) or will initially respond but later progress, indicating a need for novel treatment options for these patients [3, 4].

Trophoblast cell-surface antigen 2 (TROP2) is a transmembrane glycoprotein that is highly expressed in many cancer types, including breast cancer [5–8]. High TROP2 expression has been associated with cancer proliferation, migration, invasion, and metastasis and with poor prognosis [5, 7], suggesting TROP2 may be a target for anticancer therapy. This is supported by sacituzumab govitecan, an antibody–drug conjugate (ADC) comprising an anti-TROP2 antibody coupled to the toxic payload SN-38 (the active metabolite of irinotecan and a topoisomerase I inhibitor) that is approved for previously treated, unresectable, locally advanced or metastatic TNBC and HR+/HER2– breast cancer [9–11].

Sacituzumab tirumotecan (sac-TMT; also known as MK-2870/SKB264) is a TROP2-directed ADC that is composed of a humanized anti-TROP2 monoclonal antibody, a sulfonyl pyrimidine-CL2A-carbonate linker to the conjugated payload, and a belotecan-derived topoisomerase I inhibitor (KL610023) [12]. Sac-TMT shares the same monoclonal antibody as sacituzumab govitecan and has a different linker and payload. This linker has been shown to improve the stability of sac-TMT through its irreversible nucleophilic aromatic substitution mechanism [12]. In preclinical studies, sac-TMT has demonstrated antitumor activity (in vitro and in vivo) in addition to preclinical safety [12].

MK-2870-001 (KL264-01) is a phase 1/2, first-in-human trial of sac-TMT as monotherapy in patients who have an unresectable locally advanced or metastatic solid tumor refractory to standard therapies. We present results from the phase 1 portion of this study and the phase 2 expansion cohorts for TNBC and HR+/HER2– breast cancer.

Methods

Study design and patients

MK-2870-001 (ClinicalTrials.gov, NCT04152499) is an open-label, phase 1/2 study of sac-TMT as monotherapy in patients in China and the United States with unresectable, locally advanced or metastatic solid tumors refractory to standard therapies. Phase 1 was the dose-finding part of the study to determine the maximum tolerated dose (MTD) and the recommended doses for expansion (RDEs) in phase 2. The RDEs were then assessed in the phase 2 cohort expansion part of the study. This manuscript describes results from phase 1 of the study and the phase 2 cohorts for metastatic TNBC (cohort 1) and HR+/HER2– breast cancer (cohort 6). This study was conducted in accordance with the Declaration of Helsinki and the International Council on Harmonization Good Clinical Practice guidelines. The protocol and its amendments were approved by an institutional review board or institutional ethics committee at each study site. Patients provided written informed consent.

In phase 1, eligible patients were 18 to 75 years old with histologically documented, incurable, locally advanced or metastatic epithelial origin cancer, including but not limited to breast cancer, ovarian epithelial cancer, non–small-cell lung cancer (NSCLC), gastric adenocarcinoma, small-cell lung cancer (SCLC), and urothelial carcinoma that is refractory to or with no available standard therapies. For phase 2, eligible patients aged ≥ 18 years with histologically or cytologically documented, incurable, locally advanced, recurrent, or metastatic cancer were enrolled into 1 of the following cohorts based on tumor type: (1) TNBC, (2) ovarian cancer, (3) NSCLC, (4) gastric adenocarcinoma/gastroesophageal junction adenocarcinoma, (5) SCLC, (6) HR+/HER2–breast cancer, (7) head and neck squamous cell carcinoma, (8) endometrial carcinoma, and (9) urothelial carcinoma. For the metastatic TNBC and HR+/HER2– breast cancer cohorts, patients must have had a tumor refractory to standard therapies or for which there were no standard therapies available. In both phase 1 and phase 2, patients must also have had measurable disease per computed tomography or magnetic resonance imaging, an Eastern Cooperative Oncology Group performance status of 0 or 1, and

adequate organ function. Further details of key eligibility criteria are provided in the Data Supplement.

Study treatment

In phase 1, sac-TMT was administered as a single intravenous infusion every 2 weeks on days 1 and 15 of each 4-week cycle at doses of 2, 4, 6, 9, and 12 mg/kg in dose-escalating cohorts. In phase 2, sac-TMT was administered every 2 weeks on days 1 and 15 of each 4-week cycle per the recommended doses identified in phase 1 of the study. Treatment continued until disease progression, unacceptable toxicity, patient withdrawal, or death.

Objectives and endpoints

The primary objectives of phase 1 were to determine the safety profile and MTD and the RDEs in phase 2 (which will not exceed the MTD). Secondary objectives for phase 1 included dose-limiting toxicities (DLTs); adverse events (AEs); characterization of the pharmacokinetics of sac-TMT ADC, sac-TMT total antibody, and free KL610023 payload; and the incidence of anti-drug antibody (ADA) formation to sac-TMT. The primary objective of phase 2 was to evaluate the objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 by investigator assessment. Secondary objectives included duration of response (DOR), progression-free survival (PFS), overall survival (OS), and safety. Definitions for these endpoints are provided in the Data Supplement.

Assessments

A DLT was defined as any of the toxicities outlined in Table S1 that were possibly, probably, or definitely related to study drug and that occurred during cycle 1 (28 days).

For the phase 1 part of the study, serum and plasma samples were collected pre-dose and at regular intervals during treatment, as detailed in the Data Supplement. Blood samples were collected for ADA evaluation before the first dose of cycles 1 to 6 and at the end-of-treatment visit.

Adverse events were assessed from the time of informed consent through 30 days after last study treatment and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. Tumor response was assessed every 8 weeks per RECIST version 1.1 by investigator review.

Statistical analysis

The sample size for phase 1 was planned for up to a total of 50 patients and in phase 2 for ~60 and ~40 patients for the TNBC and HR+/HER2– breast cancer cohorts, respectively. Dose escalation and determination of MTD in phase 1 were assessed using a Bayesian logistic regression model (BLRM) guided by the escalation with overdose control (EWOC) principle [13]. A BLRM was run at the end of each dose-escalating cohort, and the decision to escalate or deescalate dose was made by a safety review committee. Dose recommendations were based on summaries of posterior distribution of model parameters and the posterior distribution of DLT rates, including the mean, 95% credibility interval, and the probability that the true DLT rate for each dose lies in one of the following categories: 0% to 16%, underdosing; 16% to 33%, targeted toxicity; and 33% to 100%, overdosing. Following the EWOC principle, after each dose level, the recommended phase 2 dose was the dose with the highest posterior probability of DLT in the target interval (16%–33%) and the overdosing probability was < 25%.

Efficacy and safety outcomes were evaluated in all patients who received ≥ 1 dose of study drug. Baseline patient characteristics, efficacy, and safety variables were summarized descriptively. Point estimates for ORR and 95% CIs were calculated using the Clopper-Pearson method for each cohort. DOR, PFS, and OS were estimated using the Kaplan–Meier method, and median values with 2-sided 95% CIs are provided. The database cutoff date was June 29, 2023.

Results

Phase 1

Patients

Thirty patients were enrolled across 10 sites between March 16, 2020, and November 1, 2021, and received ≥ 1 dose of sac-TMT study treatment: 2 mg/kg, $n = 4$; 4 mg/kg, $n = 7$; 5 mg/kg, $n = 7$; 5.5 mg/k, $n = 5$; 6 mg/kg, $n = 7$. At the time of database cutoff, all patients had discontinued study treatment, primarily due to progressive disease (Figure S1). The enrolled patients included TNBC, HR+/HER2– breast cancer, ovarian cancer, pancreatic cancer, urothelial carcinoma, NSCLC, gastric or gastroesophageal junction cancer, and endometrial cancer, as summarized in Table 1. The median time from first study dose to database cutoff across all patients was 29.9 (range, 19.9–39.5) months.

Safety

The median (range) duration of treatment exposure was 2.8 (0–9) months in the total cohort, 2.1 (1–5) months in the 2-mg/kg group, 4.5 (1–9) months in the 4-mg/kg group, 1.0 (0–5) months in the 5-mg/kg group, 3.3 (2–5) months in the 5.5-mg/kg group, and 2.6 (0–9) months in the 6-mg/kg group. Overall, 5 patients had DLTs; 1 patient (14%) in the 4-mg/kg group had grade 3 stomatitis,

Table 1 Patient demographics and baseline disease characteristics in phase 1

Characteristic	sac-TMT treatment group					
	2 mg/kg *n* = 4	4 mg/kg *n* = 7	5 mg/kg *n* = 7	5.5 mg/kg *n* = 5	6 mg/kg *n* = 7	Total *N* = 30
Age, median (range), y	44 (42–57)	66 (32–72)	48 (38–65)	66 (36–67)	62 (55–70)	56 (32–72)
Sex						
Men	0	2 (29)	0	0	2 (29)	4 (13)
Women	4 (100)	5 (71)	7 (100)	5 (100)	5 (71)	26 (87)
ECOG performance status						
0	2 (50)	1 (14)	2 (29)	0	3 (43)	8 (27)
1	2 (50)	6 (86)	5 (71)	5 (100)	4 (57)	22 (73)
Race						
Asian	2 (50)	1 (14)	5 (71)	3 (60)	4 (57)	15 (50)
Black	0	0	0	0	1 (14)	1 (3)
White	1 (25)	5 (71)	2 (29)	2 (40)	2 (29)	12 (40)
Other	1 (25)	1 (14)	0	0	0	2 (7)
Region						
China	1 (25)	1 (14)	4 (57)	3 (60)	4 (57)	13 (43)
USA	3 (75)	6 (86)	3 (43)	2 (40)	3 (43)	17 (57)
Baseline tumor burden						
Participants with data[a], n	4	7	7	5	7	30
Tumor burden, median (range), mm	33.70 (32.0–130.0)	105.00 (34.0–211.0)	88.70 (25.0–121.6)	53.00 (34.0–112.0)	70.50 (33.3–220.0)	85.35 (25.0–220.0)

Data are expressed as n (%) unless otherwise specified

ECOG Eastern Cooperative Oncology Group, *sac-TMT* sacituzumab tirumotecan

[a] Participants with data is the number of participants with measurable target lesion(s) at baseline

1 patient (14%) in the 5-mg/kg group had grade 3 rash, 1 patient (20%) in the 5.5-mg/kg group had grade 3 stomatitis, and 2 patients (29%) in the 6-mg/kg group had grade 3 urticaria or grade 3 stomatitis (Table S2). Based on the DLT assessment criteria and the safety profile (described below; Table 2), no further dose escalation occurred beyond 6 mg/kg and the MTD was 5.5 mg/kg.

Overall, 28 patients (93%) reported ≥ 1 AE, all deemed to be treatment-related per the investigators. These were grade 3 or 4 in 17 patients (57%); none were grade 5. The most common treatment-related AEs (TRAEs) were nausea (63%), alopecia (57%), and anemia (50%). There was only 1 patient who discontinued treatment because of a TRAE: 1 patient in the 2-mg/kg group due to grade 2 treatment-related pneumonitis, as assessed by the investigator. This patient had radiation pneumonitis and received steroid treatment before enrollment. Additionally, pneumonia was also reported in this patient during the period with the treatment-related pneumonitis event. Overall, TRAEs led to treatment interruption in 13 patients and dose reduction in 6 patients, and the most commonly occurring TRAEs included nausea, alopecia, anemia, stomatitis, and vomiting (Table 2).

Pharmacokinetics and ADA formation

On day 1 of cycle 1, the plasma concentration (area under the concentration–time curve) increased for sac-TMT ADC, total antibody, and the payload (KL610023) with increasing doses. After a single infusion of sac-TMT, the maximum observed serum or plasma concentration (C_{max}) ranged from 51.5 to 147.0 μg/mL for sac-TMT ADC, 46.7 to 144.0 μg/mL for sac-TMT total antibody, and 7.2 to 31.3 ng/mL for KL610023 across the dose groups; additional pharmacokinetic parameters and plasma concentration–time profiles are provided in Table S3 and Figure S2.

Three patients in the 4-mg/kg dose group, 1 patient in the 5.5-mg/kg dose group, and 1 patient in the 6-mg/kg dose group had ≥ 1 positive ADA test after the first dose of sac-TMT.

Recommended phase 2 dose

Given the DLT data, the AE profile, and the pharmacokinetics data, the RDEs were selected as 4 mg/kg and 5 mg/kg and further explored in the phase 2 expansion cohorts.

Table 2 Summary of treatment-related AEs in phase 1

Treatment-related AE	sac-TMT treatment group											
	2 mg/kg ***n*** **= 4**		**4 mg/kg** ***n*** **= 7**		**5 mg/kg** ***n*** **= 7**		**5.5 mg/kg** ***n*** **= 5**		**6 mg/kg** ***n*** **= 7**		**Total** ***N*** **= 30**	
Any	4 (100)		7 (100)		5 (71)		5 (100)		7 (100)		28 (93)	
Grade 3 or 4[a]	0		3 (43)		4 (57)		4 (80)		6 (86)		17 (57)	
Grade 5[a]	0		0		0		0		0		0	
Serious	1 (25)		0		0		1 (20)		4 (57)		6 (20)	
Led to treatment interruption[b]	1 (25)		2 (29)		1 (14)		4 (80)		5 (71)		13 (43)	
Led to dose reduction	0		1 (14)		0		2 (40)		3 (43)		6 (20)	
Led to dose discontinuation	1 (25)		0		0		0		0		1 (3)	
Led to dose modification	1 (25)		3 (43)		1 (14)		4 (80)		6 (86)		15 (50)	
Occurring in ≥20% of patients in the total population[a]	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Nausea	3 (75)	0	6 (86)	0	4 (57)	0	2 (40)	0	4 (57)	0	19 (63)	0
Alopecia	2 (50)	0	5 (71)	0	2 (29)	0	3 (60)	0	5 (71)	0	17 (57)	0
Anemia	0	0	3 (43)	1 (14)	4 (57)	2 (29)	4 (80)	3 (60)	4 (57)	2 (29)	15 (50)	8 (27)
Stomatitis	0	0	3 (43)	1 (14)	4 (57)	1 (14)	4 (80)	2 (40)	3 (43)	1 (14)	14 (47)	5 (17)
Vomiting	1 (25)	0	4 (57)	0	3 (43)	0	1 (20)	0	5 (71)	0	14 (47)	0
Decreased neutrophil count	1 (25)	0	2 (29)	1 (14)	1 (14)	0	4 (80)	1 (20)	5 (71)	5 (71)	13 (43)	7 (23)
Fatigue	1 (25)	0	3 (43)	0	2 (29)	0	1 (20)	0	4 (57)	0	11 (37)	0
Rash	0	0	1 (14)	0	5 (71)	1 (14)	1 (20)	0	4 (57)	0	11 (37)	1 (3)
Decreased white blood cell count	0	0	1 (14)	0	2 (29)	0	3 (60)	0	5 (71)	5 (71)	11 (37)	5 (17)
Decreased platelet count	0	0	0	0	1 (14)	0	3 (60)	1 (20)	5 (71)	3 (43)	9 (30)	4 (13)
Decreased appetite	1 (25)	0	1 (14)	0	3 (43)	0	1 (20)	0	1 (14)	0	7 (23)	0
Increased ALT	1 (25)	0	1 (14)	0	1 (14)	0	3 (60)	0	0	0	6 (20)	0

Data are expressed as n (%)

AE adverse event, *ALT* alanine aminotransferase, *sac-TMT* sacituzumab tirumotecan

[a] Per the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 [b]Treatment-related AEs led to treatment interruption in the 2-mg/kg group in 1 patient due to neutropenia; in the 4-mg/kg group in 2 patients due to decreased neutrophil count ($n = 1$) and stomatitis ($n = 1$); in the 5-mg/kg group in 1 patient due to stomatitis and decreased weight; in the 5.5-mg/kg group, in 4 patients due to anemia ($n = 3$), decreased neutrophil count ($n = 2$), and stomatitis ($n = 1$); and in the 6-mg/kg group, in 5 patients due to decreased white blood cell count ($n = 4$), decreased platelet count ($n = 3$), decreased neutrophil count ($n = 3$), anemia ($n = 2$), increased blood creatinine ($n = 1$), and maculopapular rash ($n = 1$)

Table 3 Patient demographics and baseline disease characteristics in phase 2

Patient demographics and characteristics	TNBC			HR+/HER2– BC
	sac-TMT 4 mg/kg *n* = 23	sac-TMT 5 mg/kg *n* = 36	Total *N* = 59	sac-TMT 5 mg/kg *N* = 41
Age, median (range), y	48.0 (35–67)	49.0 (31–73)	49.0 (31–73)	50.0 (34–66)
Female	23 (100)	36 (100)	59 (100)	41 (100)
Male	0	0	0	0
Region of enrollment				
China	23 (100)	36 (100)	59 (100)	41 (100)
USA	0	0	0	0
ECOG performance status				
0	3 (13)	12 (33)	15 (25)	16 (39)
1	20 (87)	24 (67)	44 (75)	25 (61)
Prior therapy regimens, n				
Adjuvant/neoadjuvant	6 (26)	7 (19)	13 (22)	5 (12)
1	0	2 (6)	2 (3)	0
2	2 (9)	4 (11)	6 (10)	0
3	6 (26)	6 (17)	12 (20)	3 (7)
4	5 (22)	11 (31)	16 (27)	7 (17)
≥ 5	10 (43)	13 (36)	23 (39)	31 (76)

Data are n (%) unless otherwise noted

ECOG Eastern Cooperative Oncology Group, *HR+/HER2– BC* hormone receptor–positive/human epidermal growth factor receptor 2–negative breast cancer, *sac-TMT* sacituzumab tirumotecan, *TNBC* triple-negative breast cancer

Phase 2

Patients

In total, 59 patients were included in the TNBC cohort and received sac-TMT 4 mg/kg (n = 23) or 5 mg/kg (n = 36). The HR+/HER2– breast cancer cohort had 41 patients, all of whom received sac-TMT 5 mg/kg. Demographics and baseline disease characteristics for each cohort are provided in Table 3.

At the time of data cutoff (June 29, 2023), 3 patients (5%) in the TNBC cohort (4 mg/kg, n = 1; 5 mg/kg, n = 2) and 10 patients (24%) in the HR+/HER2– breast cancer cohort were still receiving study treatment; all other patients had

Table 4 ORR[a] and summary of tumor response in phase 2

	TNBC			HR+/HER2– BC
	sac-TMT 4 mg/kg *n* = 23	sac-TMT 5 mg/kg *n* = 36	Total *N* = 59	sac-TMT 5 mg/kg *N* = 41
ORR[a] (95% CI), %	34.8 (16.4–57.3)	38.9 (23.1–56.5)	37.3 (25.0–50.9)	31.7 (18.1–48.1)
Best overall response, n (%)				
CR	0	2 (5.6)	2 (3.4)	0
PR	8 (34.8)	12 (33.3)	20 (33.9)	13 (31.7)
SD	8 (34.8)	15 (41.7)	23 (39.0)	21 (51.2)
PD	5 (21.7)	6 (16.7)	11 (18.6)	4 (9.8)
Not evaluable[b]	0	0	0	0
No assessment[c]	2 (8.7)	1 (2.8)	3 (5.1)	3 (7.3)
Median duration of response[d] (range), mo	11.5 (5.4–22.1+)	11.5 (3.7–19.3+)	11.5 (3.7–22.1+)	9.5 (4.2–17.0+)

"+" indicates a censored observation

CR complete response, *HR+/HER2– BC* hormone receptor–positive/human epidermal growth factor receptor 2–negative breast cancer, *ORR* objective response rate, *PD* progressive disease, *PR* partial response, *sac-TMT* sacituzumab tirumotecan *SD* stable disease, *TNBC* triple-negative breast cancer

[a] ORR includes the proportion of patients with a CR or PR based on investigator assessment per RECIST version 1.1

[b] Not evaluable includes patients with insufficient data for assessment of response per RECIST version 1.1

[c] No assessment includes subjects without postbaseline assessment on the data cutoff date

[d] Time from the date of first CR or PR to the first of PD or death from any cause in patients who had CR or PR

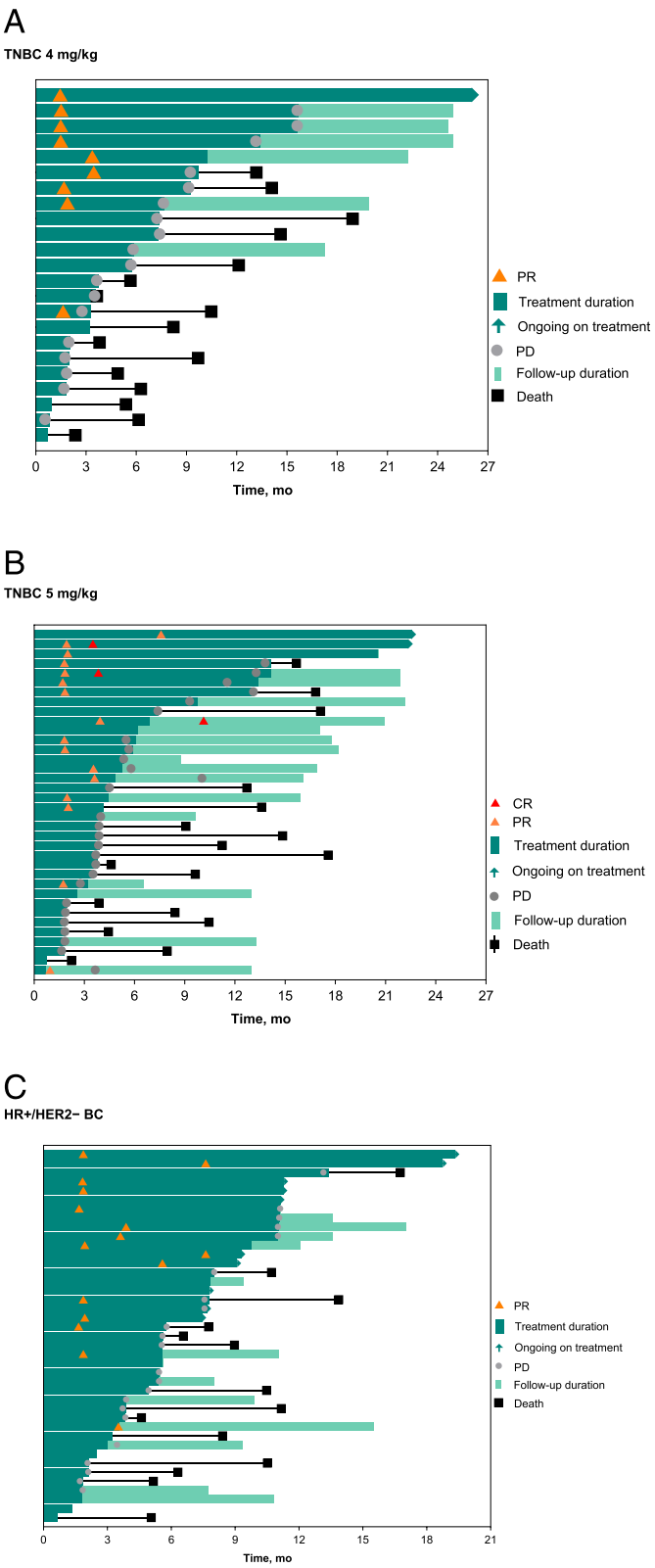

Fig. 1 Time on study treatment and treatment response in patients with an objective response. **A** TNBC, sac-TMT 4 mg/kg; (**B**) TNBC, sac-TMT 5 mg/kg; (**C**) HR+/HER2− BC. CR, complete response; HR+/HER2− BC, hormone receptor–positive/human epidermal growth factor receptor 2–negative breast cancer; PD, progressive disease; PR, partial response; sac-TMT, sacituzumab tirumotecan; TNBC, triple-negative breast cancer

discontinued study treatment (Figure S3). Median (range) time from first dose to database cutoff date was 23.1 (21.0–27.1) months in the TNBC cohort and 11.7 (7.1–19.6) months in the HR+/HER2– breast cancer cohort.

Efficacy

Metastatic TNBC The ORR was 37% across all patients, 35% in the 4-mg/kg group, and 39% in the 5-mg/kg group. Median (range) DOR was 11.5 (5.4–22.1+) and 11.5 (3.7–19.3+) months, respectively (Table 4; Figs. 1A and 1B; Fig. 2A). Median PFS was 5.7 months among all patients, 5.8 months in the 4-mg/kg group, and 5.5 months in the 5-mg/kg group (Fig. 3). Median OS was 15.7, 12.1, and 17.1 months, respectively (Fig. 3).

HR+/HER2– breast cancer The ORR in this cohort was 32%. Median (range) DOR was 9.5 (4.2–17.0+) months (Table 4, Fig. 1C, Fig. 2B). Median PFS was 8.0 months (Fig. 3). Median OS was 13.9 months (Fig. 3).

Safety

Metastatic TNBC The median (range) duration of treatment exposure was 5.3 (0–26) months in the 4-mg/kg group and 3.6 (0–22) months in the 5-mg/kg group. All patients reported ≥1 TRAE. Thirty-six patients (61%) reported grade 3 or 4 TRAEs, including 12 (52%) in the 4-mg/kg group and 24 (67%) in the 5-mg/kg group; none were grade 5. The most common TRAEs in both dosing groups were anemia (4 mg/kg, 74%; 5 mg/kg, 89%), decreased white blood cell count (4 mg/kg, 74%; 5 mg/kg, 78%), and decreased neutrophil count (4 mg/kg, 61%; 5 mg/kg, 72%; Table 5).

HR+/HER2– breast cancer Median (range) duration of treatment exposure was 5.0 (0–19) months. All 41 patients reported ≥1 TRAE, including 22 (54%) with grade 3 or 4 TRAEs. There were no grade 5 TRAEs. The most common TRAEs were decreased white blood cell count (n = 36 [88%]), anemia, and decreased neutrophil count (both n = 35 [85%]; Table 5).

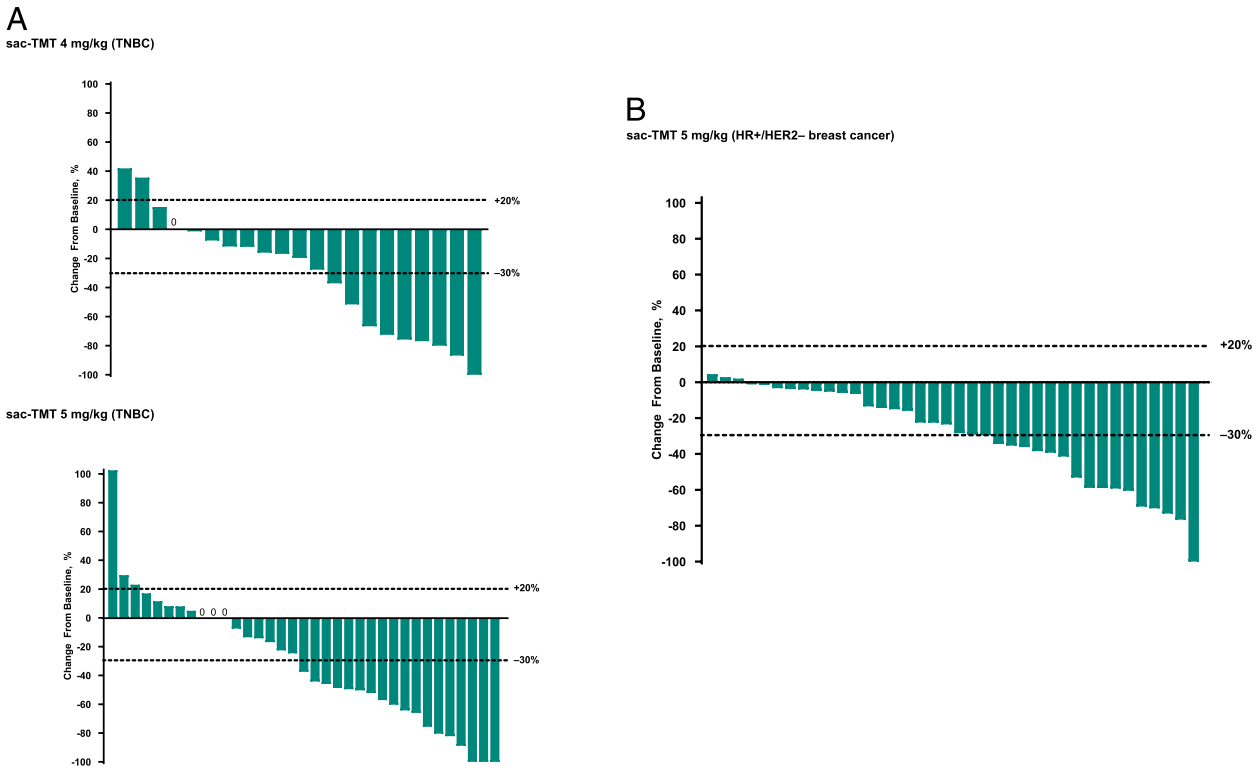

Fig. 2 Best change from baseline in size of tumor lesions following treatment with sac-TMT in the (**A**) TNBC cohort and (**B**) HR+/HER2– breast cancer cohort in the dose expansion phase. HR+/HER2–, hormone receptor–positive/human epidermal growth factor receptor 2–negative; sac-TMT, sacituzumab tirumotecan; TNBC, triple-negative breast cancer

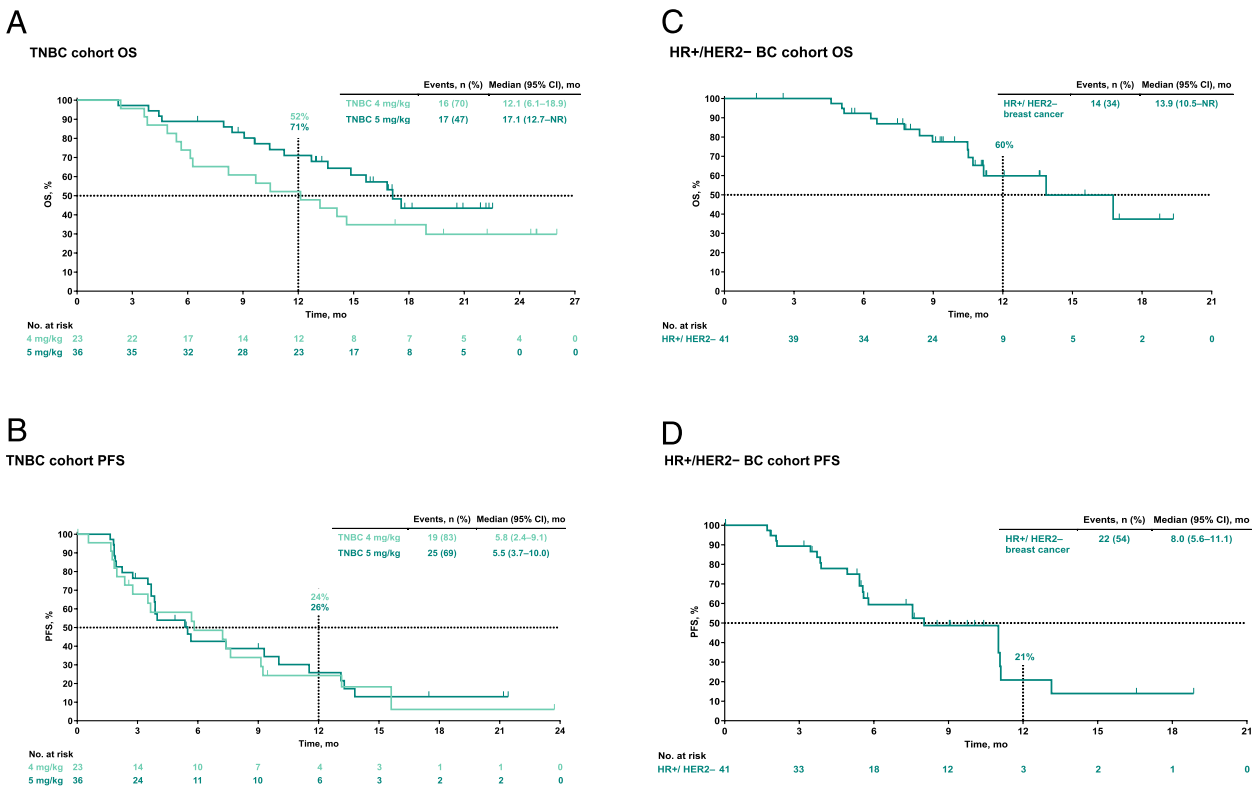

Fig. 3 Kaplan–Meier estimates of (**A**) OS in the TNBC cohort, (**B**) PFS in the TNBC cohort, (**C**) OS in the HR+/HER2− BC cohort, and (**D**) PFS in the HR+/HER2− BC cohort. PFS is defined as the time from first infusion of study drug to documented disease progression or death from any cause, whichever occurred first. OS is defined as the time from first infusion of study drug until death from any cause. HR+/HER2− BC, hormone receptor–positive/human epidermal growth factor receptor 2–negative breast cancer; NR, not reached; OS, overall survival; PFS, progression-free survival; TNBC, triple-negative breast cancer

Discussion

This manuscript describes the results from the first-in-human trial of sac-TMT as monotherapy in patients with an unresectable locally advanced or metastatic solid tumor that is refractory to standard therapies. In this study, treatment with sac-TMT was associated with a manageable toxicity profile and promising antitumor activity.

In the phase 1 dose-finding portion of the study, sac-TMT did not exceed the DLT target threshold at doses of 2, 4, 5, and 5.5 mg/kg and doses were escalated accordingly. At 6 mg/kg dosing, 29% of patients had DLTs of grade 3 urticaria and stomatitis. Additionally, due to the higher incidence of TRAEs that led to treatment interruption and serious TRAEs at sac-TMT 6 mg/kg, dose escalation was stopped at 6 mg/kg. As a result, the MTD was established as 5.5 mg/kg. Across all dose groups, the most common TRAEs were nausea, alopecia, and anemia. The incidence of treatment-related grade 3 and 4 AEs increased at higher doses; however, there were no grade 5 TRAEs in any dosing group.

During phase 1, sac-TMT demonstrated a generally linear pharmacokinetic profile in which the half-life of sac-TMT ADC was longest and plasma/serum concentration of the payload (KL610023) was highest at 5 mg/kg after a single intravenous infusion of sac-TMT. Given the comparatively higher toxicity at 5.5 mg/kg compared with lower dosing and the favorable pharmacokinetics profile, sac-TMT 4 mg/kg and 5 mg/kg were chosen for RDEs.

In the phase 2 cohort expansion of the study, sac-TMT demonstrated promising antitumor activity and a manageable AE profile in patients with heavily pretreated TNBC and HR+/HER2− breast cancer. Patients with metastatic TNBC received sac-TMT at 4 or 5 mg/kg. Both doses were associated with promising antitumor activity, albeit 5 mg/kg may be associated with slightly higher toxicity than 4 mg/kg. Overall, AEs were manageable in both dosing groups and the most commonly observed TRAEs were hematologic: anemia, decreased white blood cell count, and decreased neutrophil count. These observed AEs are consistent with those expected with the belotecan payload (KL610023) of sac-TMT [12]. These findings have recently been corroborated in the randomized phase 3 OptiTROP-Breast01 study, in which sac-TMT 5 mg/kg was associated with an ORR of 44% versus 13% with chemotherapy and demonstrated statistically significant improvements in PFS (hazard ratio,

Table 5 Summary of treatment-related AEs in phase 2 in all treated patients

Treatment-related AE	TNBC						HR+/HER2– BC	
	sac-TMT 4 mg/kg *n* = 23		sac-TMT 5 mg/kg *n* = 36		Total *N* = 59		sac-TMT 5 mg/kg *N* = 41	
Any	23 (100)		36 (100)		59 (100)		41 (100)	
Grade 3 or 4[a]	12 (52)		24 (67)		36 (61)		22 (54)	
Grade 5[a]	0		0		0		0	
Led to treatment interruption	9 (39)		21 (58)		30 (51)		13 (32)	
Led to dose reduction	2 (9)[b]		6 (17)[c]		8 (14)[b,c]		7 (17)[d]	
Led to dose discontinuation	1 (4)[e]		2 (6)[f]		3 (5)[e,f]		1 (2)[g]	
Occurring in ≥ 40% of patients in either treatment group of any cohort[a]	**Any Grade**	**Grade ≥ 3**	**Any Grade**	**Grade ≥ 3**	**Any Grade**	**Grade ≥ 3**	**Any Grade**	**Grade ≥ 3**
Anemia	17 (74)	4 (17)	32 (89)	9 (25)	49 (83)	13 (22)	35 (85)	8 (20)
Decreased white blood cell count	17 (74)	3 (13)	28 (78)	11 (31)	45 (76)	14 (24)	36 (88)	9 (22)
Decreased neutrophil count	14 (61)	2 (9)	26 (72)	13 (36)	40 (68)	15 (25)	35 (85)	17 (41)
Stomatitis	6 (26)	1 (4)	21 (58)	3 (8)	27 (46)	4 (7)	22 (54)	1 (2)
Decreased platelet count	5 (22)	3 (13)	18 (50)	8 (22)	23 (39)	11 (19)	17 (41)	5 (12)
Vomiting	10 (43)	0	16 (44)	0	26 (44)	0	10 (24)	0
Rash	6 (26)	0	15 (42)	2 (6)	21 (36)	2 (3)	14 (34)	0
Nausea	10 (43)	0	12 (33)	0	22 (37)	0	9 (22)	0

Data are expressed as n (%)

AE adverse event, *HR+/HER2– BC* hormone receptor–positive/human epidermal growth factor receptor 2–negative breast cancer, *sac-TMT* sacituzumab tirumotecan, *TNBC* triple-negative breast cancer

[a] Per the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0

[b] Due to decreased neutrophil count (*n* = 1), decreased white blood cell count (*n* = 1), and decreased platelet count (*n* = 1)

[c] Due to anemia (*n* = 2), decreased neutrophil count (*n* = 2), agranulocytosis (*n* = 1), myelosuppression (*n* = 1), stomatitis (*n* = 1), vomiting (*n* = 1), decreased weight (*n* = 1), and decreased white blood cell count (*n* = 1)

[d] Due to decreased neutrophil count (*n* = 4), decreased platelet count (*n* = 4), anemia (2), decreased white blood cell count (*n* = 2), and thrombocytopenia (*n* = 1)

[e] Due to an anaphylactic reaction

[f] Due to dry eye and anaphylactic shock in 1 patient each

[g] Due to anemia

0.31), and OS (hazard ratio, 0.53) for patients with TNBC and a manageable safety profile compared with chemotherapy in 263 patients with previously treated locally recurrent or metastatic TNBC [14].

Our study also demonstrated an ORR of 32%, median PFS of 8 months, and median OS of 14 months with sac-TMT in patients with previously treated HR+/HER2– breast cancer. While the follow-up period for this study is relatively short, patients continue to be monitored beyond the reported follow-up. In addition to the promising antitumor activity, sac-TMT also had a manageable safety profile, with 32% of patients reporting TRAEs that resulted in treatment interruption and only 1 patient discontinuing treatment because of a TRAE (anemia). The most common TRAEs in this cohort were also decreased white blood cell count, anemia, and decreased neutrophil count.

Similar antitumor activity has been reported with other TROP2-directed ADCs. In phase 1/2 and phase 3 studies of patients with relapsed or refractory metastatic TNBC, sacituzumab govitecan was associated with ORRs between 33% and 35%, median PFS of 5.5 to 5.6 months, and median OS of 12.1 to 13.0 months [15, 16]. Similarly, datopotamab deruxtecan (dato-DXd), a TROP2-directed ADC with deruxtecan (an exatecan derivative) as its payload, was associated with an ORR of 32% in patients with TNBC who had relapsed or progressed after prior treatment or for which no standard treatment was available. The most common TRAEs were gastrointestinal disorders and hematologic disorders, including diarrhea (59%), nausea (57%), and neutropenia (63%) with sacituzumab govitecan, that are commonly associated with an SN-38 payload [9]. The most common TRAEs with dato-DXd were gastrointestinal disorders, including stomatitis (73%), nausea (66%), and alopecia (36%) [17]. In patients with previously treated HR+/HER2– breast cancer, sacituzumab govitecan demonstrated an ORR of 31% [18]

and dato-DXd demonstrated an ORR of 27% [17]. The most commonly reported TRAEs included neutropenia (72%), nausea (67%), and fatigue (50%) for sacituzumab govitecan [18] and stomatitis (80%), nausea (51%), and fatigue (44%) for dato-DXd [17]. Altogether, the results demonstrate that sac-TMT has antitumor activity similar to sacituzumab govitecan and dato-DXd, but with a different safety profile and potentially lower incidence of hematologic disorders compared with sacituzumab govitecan [9, 15, 17], which may be attributable to differences in payload and a more stable linker [12]. However, cross-study comparisons should be made with caution given differences in study design and patient and disease characteristics.

Our study had several limitations. First, this was a relatively small, single-arm, phase 1/2 study with no comparator arm, and therefore, no statistical comparisons can be made to current standard-of-care treatment. Second, the phase 1 portion of the study included patients enrolled in both China and United States, but the dose expansion TNBC and HR+/HER2– breast cancer cohorts enrolled patients in China only, which may limit the generalizability of results across patients from other regions and ethnicities.

Additionally, biomarker analyses were not conducted in the current analyses given the relatively limited sample size; however, future studies in larger patient populations that are specifically designed to investigate this may provide further characterization of factors associated with response to sac-TMT. Based on the manageable AE profile and promising antitumor activity observed in earlier-phase studies, phase 3 studies are ongoing, including one for sac-TMT as monotherapy in unresectable, locally advanced, recurrent or metastatic HR+/HER2– breast cancer (NCT06081959) and one for sac-TMT as monotherapy and in combination with pembrolizumab in patients with HR+/HER2– unresectable locally advanced or metastatic breast cancer (NCT06312176).

Conclusions

In conclusion, sac-TMT demonstrated a manageable AE profile in patients with unresectable locally advanced or metastatic TNBC and HR+/HER2– breast cancer that is refractory to standard therapies. Based on DLT assessment in the phase 1 part of the study, the 4-mg/kg and 5-mg/kg doses were selected for further evaluation in the phase 2 portion of the study. Sac-TMT demonstrated promising antitumor activity with manageable AEs in patients with TNBC and HR+/HER2– breast cancer, supporting future assessment of sac-TMT in phase 3 trials.

Abbreviations

ADA	Anti-drug antibody
ADC	Antibody-drug conjugate
AE	Adverse event
BLRM	Bayesian logistic regression model
C_{max}	Plasma concentration
DLT	Dose-limiting toxicity
DOR	Duration of response
EWOC	Escalation with overdose control
HER2–	Human epidermal growth factor receptor 2 negative
HR+	Hormone receptor positive
MTD	Maximum tolerated dose
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSCLC	Non–small-cell lung cancer
ORR	Objective response rate
OS	Overall survival
PFS	Progression-free survival
RDE	Recommended doses for expansion
RECIST	Response Evaluation Criteria in Solid Tumors
Sac-TMT	Sacituzumab tirumotecan
SCLC	Small-cell lung cancer
TNBC	Triple-negative breast cancer
TRAE	Treatment-related adverse event
TROP2	Trophoblast cell-surface antigen 2

Supplementary Information

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Supplementary Material 1.

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Authors' contributions

All authors had access to study data, and reviewed, revised, and approved the final manuscript. AS was also involved in conception, design, and planning of the study, data acquisition, data analysis, interpretation of results, provision of study materials/patients, and administrative, logistical or technical support. CG, JSW, OO, X. Wu, Y. Liang, and ZT were also involved in data acquisition, and interpretation of results. EC, and OOA were involved in data analysis, and interpretation of results. GL, JG, YPL, and Y. Li were also involved in conception, design, and planning of the study, data analysis, and interpretation of results. GY, JR, LS, MRS, QL, WZ, YC, and YW were also involved in data acquisition, interpretation of results, and provision of study materials/patients. MY was also involved in conception, design, and planning of the study, interpretation of results, and provision of study materials/patients. RES was also involved in data acquisition, and provision of study materials/patients. SVU was also involved in data acquisition, data analysis, and interpretation of results. X. Wang was also involved in data acquisition. YC, and YW were also involved in data acquisition, interpretation of results, and provision of study materials/patients. YY was involved in conception, design, and planning of the study, data acquisition, data analysis, and interpretation of results. ZAW was involved in data analysis, interpretation of results, and provision of study materials/patients.

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Data availability

Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (MSD) is committed to providing qualified scientific researchers access to anonymized data and clinical study reports from the company's clinical trials for the purpose of conducting legitimate scientific research. MSD is also obligated to protect the rights and privacy of trial participants and, as such, has a

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Declarations

Ethics approval and consent to participate

The protocol and its amendments were approved by an institutional review board or institutional ethics committee at each study site, including the University of Texas MD Anderson Cancer Center Institutional Review Board (IRB 1 IRB00000121) and the Medical Ethics Committee of Shanghai East Hospital Affiliated to Tongii University School of Medicine (2020 [015]).

Competing interests

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