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ORIGINAL ARTICLE

Safety, pharmacokinetics, and antitumor activity of the anti-CEACAM5-DM4 antibody—drug conjugate tusamitamab ravtansine (SAR408701) in patients with advanced solid tumors: first-in-human dose-escalation study

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Background: Tusamitamab ravtansine (SAR408701) is an antibody—drug conjugate composed of a humanized monoclonal antibody that binds carcinoembryonic antigen-related cell adhesion molecule-5 (CEACAM5) and a cytotoxic maytansinoid that selectively targets CEACAM5-expressing tumor cells. In this phase I dose-escalation study, we evaluated the safety, pharmacokinetics, and preliminary antitumor activity of tusamitamab ravtansine in patients with solid tumors.

Patients and methods: Eligible patients were aged ≥18 years, had locally advanced/metastatic solid tumors that expressed or were likely to express CEACAM5, and had an Eastern Cooperative Oncology Group Performance Status of 0 or 1. Patients were treated with ascending doses of tusamitamab ravtansine intravenously every 2 weeks (Q2W). The first three dose levels (5, 10, and 20 mg/m^2) were evaluated using an accelerated escalation protocol, after which an adaptive Bayesian procedure was used. The primary endpoint was the incidence of dose-limiting toxicities (DLTs) during the first two cycles, graded using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03 criteria.

Results: Thirty-one patients received tusamitamab ravtansine (range 5-150 mg/m^2). The DLT population comprised 28 patients; DLTs (reversible grade 3 microcystic keratopathy) occurred in three of eight patients treated with tusamitamab ravtansine 120 mg/m^2 and in two of three patients treated with 150 mg/m^2. The maximum tolerated dose was identified as 100 mg/m^2. Twenty-two patients (71%) experienced ≥1 treatment-related treatment-emergent adverse event (TEAE), seven patients (22.6%) experienced ≥1 treatment-related grade ≥3 TEAE, and three patients (9.7%) discontinued treatment due to TEAEs. The most common TEAEs were asthenia, decreased appetite, keratopathy, and nausea. Three patients had confirmed partial responses. The mean plasma exposure of tusamitamab ravtansine increased in a dose-proportional manner from 10 to 150 mg/m^2.

Conclusions: Tusamitamab ravtansine had a favorable safety profile with reversible, dose-related keratopathy as the DLT. Based on the overall safety profile, pharmacokinetic data, and Bayesian model recommendations, the maximum tolerated dose of tusamitamab ravtansine was defined as 100 mg/m^2 Q2W.

Key words: antibody—drug conjugate, carcinoembryonic antigen-related cell adhesion molecule-5, dose-escalation study, dose-limiting toxicity, maytansinoid, tusamitamab ravtansine

INTRODUCTION

Carcinoembryonic antigen (CEA)-related cell adhesion molecule 5 (CEACAM5, also known as CD66e), a cell surface glycoprotein, is weakly expressed in normal epithelial tissues including colon, esophagus, head and neck, stomach, and cervix tissue but is highly expressed in several tumor types including gastrointestinal, lung, and breast.[1,2] In normal tissue, CEA protects luminal organs from microbial

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invasion. In tumor cells, CEACAM5 plays a contact-mediating role during metastasis[3] and facilitates tumor invasion and metastasis.[4] Hence, the differential expression of CEACAM5 in tumor versus normal tissue makes it an attractive therapeutic target.[5]

Expression of CEACAM5 may correlate with prognosis in some tumor types. For example, in patients with stage I, II, and III colorectal cancer, 5-year survival was inversely correlated with tissue expression of CEACAM5, and in patients with stage III disease, increased serum levels of CEACAM5 were associated with poor prognosis.[4]

Linking potent cytotoxic drugs to monoclonal antibodies creates antibody—drug conjugates (ADCs) with high tumor specificity and increased cytotoxic potential.[5] Tusamitamab ravtansine (SAR408701) is a potential first-in-class ADC that selectively targets CEACAM5-expressing tumor cells and comprises a humanized monoclonal antibody (SAR408377), which is highly specific for the extracellular domain of human and cynomolgus monkey CEACAM5, covalently linked to a potent cytotoxic maytansinoid (DM4) by a cleavable N-succinimidyl 4-(2-pyridyldithio) butyrate (SPDB) linker.[6] The drug-to-antibody ratio for the ADC is 3.8.[7] Tusamitamab ravtansine binding to the CEACAM5 extracellular domain is followed by its internalization, the cleavage of the disulfide linker, and the release of DM4 into the tumor cell. DM4 subsequently inhibits microtubule assembly resulting in cell cycle arrest and apoptosis.[7,8] The thiol compound DM4 is also subsequently S-methylated by cellular methyltransferase activity to form S-methyl-DM4, which is also highly cytotoxic. Both DM4 and S-methyl-DM4 can cross the membrane and lead to a target-enhanced 'bystander effect' in which cytotoxicity can be seen in both target-expressing and non-expressing neighboring cells.[9]

Tusamitamab ravtansine has antitumor activity in CEACAM5-expressing tumor cell lines and patient-derived xenograft models.[2] Building on these promising preclinical results, a model-based approach was used to select potential phase I dosing regimens, which informed the design of the present first-in-human study.[6] Here we describe the safety, pharmacokinetics (PK), preliminary antitumor activity, and the maximum tolerated dose (MTD) of tusamitamab ravtansine.

METHODS

Study design

This phase I trial in patients with advanced solid tumors comprised dose-escalation and dose-expansion phases; only the main dose-escalation phase is presented here. The study was conducted in accordance with the Declaration of Helsinki, International Conference on Harmonisation, and Good Clinical Practice. The protocol and all amendments were reviewed and approved by the presiding institutional review board or ethics committee at each participating center. All patients provided written informed consent before participating in the trial. Clinical trial number: Clinicaltrials.gov NCT02187848.

Study population

Patients eligible for the dose-escalation phase were at least 18 years of age with locally advanced/metastatic solid malignant tumors for which no standard alternative therapy was available and had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1. The study population was enriched for patients with tumors that expressed or were likely to express CEACAM5 (Supplementary Material, available at https://doi.org/10.1016/j.annonc.2021.12.012), or who had a circulating CEA level >5 ng/ml as determined by local laboratories. Tumor CEACAM5 expression was retrospectively documented from archival formalin-fixed paraffin-embedded tissue specimens by a central laboratory using immunohistochemistry (IHC; Supplementary Material, available at https://doi.org/10.1016/j.annonc.2021.12.012). Response Evaluation Criteria for Solid Tumors (RECIST) measurable target lesions were not required.

Patients were excluded if they had a life expectancy <12 weeks, had known or symptomatic brain metastasis, were receiving any other cancer treatment, had previously received therapy targeting CEACAM5, had prior maytansinoid treatments (i.e. DM1 or DM4 antibody conjugates), or had poor bone marrow reserve or major organ dysfunction.

Treatment

Tusamitamab ravtansine was administered intravenously. In the main dose-escalation cohort, tusamitamab ravtansine was given in an every-2-weeks (Q2W) cycle. The protocol specified that tusamitamab ravtansine was to be administered over nine potential dose levels (DLs) ranging from 5 to 210 mg/m^2 (Figure 1). The starting dose, defined as one-sixth of the highest non-severe toxic dose in non-rodent species,[10] was estimated based on the starting doses evaluated for the once-per-week (4 mg/m^2) and once-every-3-weeks (10 mg/m^2) schedules in non-human primates, which suggested that the dose of 5 mg/m^2 would be safe in patients using a Q2W schedule. The first three DLs of tusamitamab ravtansine (5 mg/m^2, 10 mg/m^2, and 20 mg/m^2) were evaluated using an accelerated escalation protocol, with one patient per dose level. Accelerated escalation could be stopped at the first dose level at which any treatment-related grade ≥ 2 adverse event (AE) or dose-limiting toxicity (DLT) was reported in the first two cycles. Subsequent dose escalations used an adaptive Bayesian procedure in cohorts of at least three patients (escalation with overdose control; Supplementary Material, available at https://doi.org/10.1016/j.annonc.2021.12.012). Patients continued treatment until disease progression, unacceptable toxicity, or patient/physician decision to discontinue.

Tusamitamab ravtansine was infused at a rate of 2.5 mg/min for the first 30 minutes and then 5 mg/min in the absence of hypersensitivity reactions. The infusion time ranged from 3 minutes to 1.5 hours depending on the total dose to be administered.

All patients received an oral antihistamine (e.g. diphenhydramine 50 mg) 1 hour before administration of tusamitamab ravtansine to prevent hypersensitivity reactions.

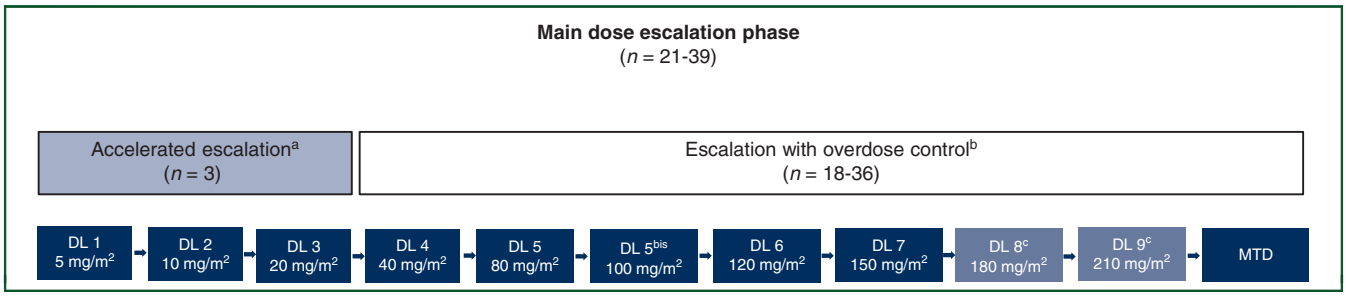

Figure 1. Dose-escalation schematic.
[a]During the accelerated escalation phase, the occurrence of toxicities observed in cycle 1 and cycle 2 of treatment was assessed in one patient.
[b]As soon as a related grade ≥2 AE or DLT occurred at an accelerated escalation DL (DL1, 2, or 3, whichever occurred first), or from DL4, the Bayesian escalation with overdose control escalation strategy was initiated with evaluation of at least three patients/cohort.
[c]Dose escalation was terminated before reaching these DLs. DL5[bis] was an optional dose level.
AE, adverse event; DL, dose level; DLT, dose-limiting toxicity; MTD, maximum tolerated dose.

During the trial, the protocol was amended to implement ocular prophylactic measures to mitigate corneal DLTs. This included the application of a vasoconstrictor (e.g. phenylephrine 2.5% ophthalmic solution) before each infusion; application of an ocular corticosteroid gel three times daily for 2 days starting on the day of the infusion; and use of cold masks or pads during the infusion. All patients were advised to use prophylactic lubricating eye drops in each eye three to six times a day.

Endpoints

The primary endpoint was the incidence of DLTs occurring during the first two cycles (4 weeks) of study drug administration. DLT was defined using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03 criteria. Hematological toxicities considered to be DLTs included: grade 4 neutropenia lasting at least 7 consecutive days; febrile neutropenia or neutropenic infection (documented infection with grade ≥3 neutropenia); grade 4 thrombocytopenia; or grade 3 thrombocytopenia with bleeding requiring transfusion. Non-hematological toxicities considered to be DLTs included: grade ≥3 toxicities excluding some grade 3 events that resolved rapidly (nausea and vomiting, diarrhea, asymptomatic electrolyte disturbances, asymptomatic grade 3 aspartate aminotransferase/alanine aminotransferase increases, fatigue); grade ≥2 cardiac conduction toxicities; any tusamitamab ravtansine-related toxicity resulting in a treatment delay of >2 weeks; and any treatment-emergent AE (TEAE) that in the opinion of the Study Committee was of potential clinical significance such that further dose escalation would expose patients to unacceptable risks.

Secondary endpoints included the overall safety profile and PK properties of tusamitamab ravtansine, antitumor activity (as defined by RECIST v1.1 tumor response criteria), and immunogenicity (whether the ADC provoked an immune response).

Assessments

Safety was assessed by physical examination, laboratory tests, specific tests, and by the incidence and severity (graded by NCI CTCAE v4.03) of AEs. Ocular toxicity was assessed using specific ophthalmologic/ocular tests (Supplementary Material, available at https://doi.org/10.1016/j.annonc.2021.12.012).

Tusamitamab ravtansine plasma concentrations were determined using a validated immunoassay detecting the ADC bearing at least one DM4 molecule. PK parameters at cycle 1 were calculated by standard non-compartmental analysis.

Tumor burden was assessed by computerized tomography or magnetic resonance imaging scans at baseline. Objective response was measured in patients with disease that could be readily measured and reassessed. Tumor assessments were carried out every 8 weeks and assessed according to RECIST v1.1, with partial or complete responses requiring confirmation on a second examination done at least 4 weeks later.

Immunogenicity was assessed by the presence of anti-tusamitamab ravtansine antibodies (anti-therapeutic antibodies [ATAs]) detected by a validated enzyme-linked immunosorbent assay bridge method.

Statistical analysis for the main dose-escalation cohort

The primary objective was to determine the MTD of tusamitamab ravtansine according to DLTs observed when administered Q2W. The adaptive Bayesian dose escalation is described in the Supplementary Material, available at https://doi.org/10.1016/j.annonc.2021.12.012. Based on different simulated scenarios, it was anticipated that ∼18 to 36 DLT-assessable patients would be enrolled in the Bayesian dose-escalation DLs, and total enrollment in the main escalation cohort would be 21 to 39 patients.

The all-treated/safety population comprised all patients who received at least one dose of study medication. The DLT-assessable population comprised all patients who completed cycle 2 and received at least 80% of the intended dose of each of the first two infusions, unless they discontinued treatment before completing cycle 2 because of a DLT. All analyses were descriptive.

RESULTS

Thirty-seven patients were screened for eligibility; 31 patients were enrolled between 29 August 2014, and 16

March 2016, and treated with tusamitamab ravtansine across eight DLs ranging from 5 to 150 mg/m^2 (Table 1). At the date of this analysis (19 October 2020), all patients had discontinued treatment (28 due to disease progression and 3 due to AEs).

Baseline demographic and disease characteristics of the all-treated/safety population are presented in Table 1 by DL. At baseline, all enrolled patients had metastatic disease, the median age was 59 years, a majority were male (61.3%), had an ECOG PS of 1 (54.8%), colorectal cancer (58.1%), measurable disease (87.1%), and a circulating CEA level $\geq$ 5 ng/ml (66.7%).

Across all DLs, 174 cycles were administered to 31 patients. The median duration of treatment was 8.1 weeks, and the median number of cycles administered per patient was 4 (range 1 to 16; Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2021.12.012). Among patients in the three highest DLs (100, 120, and 150 mg/m^2), the median duration of treatment was 12 (range 4 to 34), 10 (range 2 to 28), and 11.9 (range 4.4 to 12) weeks, and the median number of cycles administered was 6 (range 2 to 16), 5 (range 1 to 11), and 4 (range 2 to 5) per patient, respectively.

Eleven patients (35.5%) had at least one dose modification and two patients (6.5%) had dose interruptions. Among 18 patients in the three highest DLs, 9 patients had at least one dose modification.

Dose-limiting toxicities

The DLT population comprised 28 patients. DLTs occurred in five patients: in three of eight patients treated with tusamitamab ravtansine 120 mg/m^2 and in two of three patients treated with 150 mg/m^2 (Table 2). In each patient, the DLT was reversible grade 3 microcystic keratopathy that occurred at the end of the second cycle and prevented enrollment to the last two potential dose levels from proceeding. Two of three patients treated with tusamitamab ravtansine 120 mg/m^2 developed microcystic keratopathy while receiving primary ocular prophylaxis. Typically, the microcystic lesions observed at slit-lamp examination were described as reflective structures at confocal microscopic examination that evolved from the periphery to the center of the cornea and were associated with blurred vision (Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2021.12.012).

On the basis of the overall safety profile, PK data, and the Bayesian model recommendations, the MTD was defined as 100 mg/m^2 Q2W.

Safety

The safety population comprised 31 patients. Overall, 29 patients (93.5%) experienced at least one TEAE, and 22 patients (71%) experienced at least one treatment-related TEAE (any grade). The most common TEAEs included asthenia,

Table 1. Baseline demographics and disease characteristics by dose level and overall (all-treated/safety population)

Characteristic	Dose of tusamitamab ravtansine (mg/m^2) administered Q2W								All patients (N = 31)
	5 (n = 2)	10 (n = 4[b])	20 (n = 1)	40 (n = 3)	80 (n = 3)	100 (n = 6)	120 (n = 9)	150 (n = 3)	
Age, years	64 (61, 67)	56.5 (52, 64)	53	52 (49, 74)	57 (44, 60)	61.5 (43, 74)	63 (48, 71)	54 (52, 60)	59 (43, 74)
Male sex, n (%)	2	4	0	0	1	6	5	1	19 (61.3)
ECOG PS score, n (%)									
0	0	2	1	0	2	3	5	1	14 (45.2)
1	2	2	0	3	1	3	4	2	17 (54.8)
Body surface area, m^2	2.1 (2.1, 2.2)	1.9 (1.8, 2.1)	1.7	1.4 (1.3, 1.6)	1.6 (1.5, 2.1)	1.8 (1.5, 2.0)	1.9 (1.7, 2.6)	1.7 (1.7, 1.8)	1.8 (1.3, 2.6)
Primary tumor location, n (%)									
Colorectal	1	2	1	1	1	3	7	2	18 (58.1)
Stomach	0	0	0	2	2	2	0	1	7 (22.6)
Gastroesophageal junction	1	2	0	0	0	0	0	0	3 (9.7)
Pancreas	0	0	0	0	0	1	0	0	1 (3.2)
Breast	0	0	0	0	0	0	1	0	1 (3.2)
Esophageal	0	0	0	0	0	0	1	0	1 (3.2)
Measurable disease, n (%)	2	3	1	3	2	5	9	2	27 (87.1)
Number of prior regimens, n	2.5 (1, 4)	3 (2, 3)	3	4 (3, 4)	3 (2, 6)	3.5 (2, 5)	3 (2, 9)	4 (2, 4)	3 (1, 9)
Prior anti-tubulin exposure, n (%)	0	1	0	2	1	2	2	1	9 (29.0)
CEACAM5 expression[a], n (%)									
<50%	1	1	0	2	2	1	3	2	12 (38.7)
50%-79%	1	2	0	1	0	1	1	1	7 (22.6)
≥80%	0	1	1	0	1	4	5	0	12 (38.7)
Circulating CEA level, n (%)									
<5 µg/l	0	0	0	2	1	3	3	1	10 (33.3)
≥5 µg/l	2	4	1	1	2	3	5	2	20 (66.7)

Values are median (minimum, maximum) unless otherwise stated.

CEA, carcinoembryonic antigen; CEACAM5, carcinoembryonic antigen-related cell adhesion molecule 5; ECOG PS, Eastern Cooperative Oncology Group Performance Status; Q2W, once every two weeks.

[a] At intensity 2+/3+ (on archival sample).

[b] Four patients were enrolled at this dose level because the first patient experienced rapid disease progression before completing two cycles and was replaced, and the second patient withdrew because of a grade 2 hypersensitivity reaction during cycles 2 and 3. The Study Committee elected to enroll two additional patients at this dose level to ensure a thorough evaluation of safety.

Table 2. Patients with at least one DLT event (DLT-assessable population)

Tusamitamab ravtansine dose level (mg/m^2)	Patients treated, *n*	Patients with DLT/patients assessable for DLT, *n/n*	DLT event in C1—C2, grade, cycle of occurrence (total cycles)	Event meeting DLT definition occurring after C1—C2, grade, cycle of occurrence (total cycles)	Outcome
5	2	0/1			
10	4	0/3			
20	1	0/1			
40	3	0/3			
80	3	0/3			
100	6	0/6		Keratopathy, G3, C12 (16)	Recovered/resolved
120	9	3/8	**Keratopathy**, G3, C2 (10)	Punctate keratitis G3, C6 (10)	Recovered/resolved
			Keratopathy, G3, C2 (11)		Recovered/resolved
			Keratopathy, G3, C2 (4)		Recovered/resolved
				Hemorrhagic erosive colitis, G4, C5 (5)	Recovered/resolved
				Neutropenia, G4, C5, (5)	Recovered/resolved
150	3	2/3	**Keratopathy**, G3, C2 (2)		Recovered/resolved
			Keratopathy, G3, C2 (4)		Recovered/resolved

Events occurring within the protocol-defined DLT observation period of two cycles are in bold.
C, cycle; DLT, dose-limiting toxicity; G, grade.

decreased appetite, keratopathy, and nausea, each of which was reported in eight patients (25.8%, Table 3).

Three patients (9.7%) discontinued treatment due to TEAEs (one each for a grade 2 hypersensitivity reaction at a DL of 10 mg/m^2, grade 4 hemorrhagic erosive colitis at a DL of 120 mg/m^2, and grade 3 keratopathy at a DL of 150 mg/m^2).

Seven patients (22.6%) experienced at least one treatment-related grade $\geq$3 TEAE, including five patients with grade 3 keratopathy during cycle 2 (three while receiving tusamitamab ravtansine 120 mg/m^2, and two while receiving 150 mg/m^2) that were characterized as DLTs and have already been described (Table 2). One patient who had grade 3 keratopathy during cycle 2 also had grade 3 punctate keratitis during cycle 6 while receiving tusamitamab ravtansine 120 mg/m^2. The dose of tusamitamab ravtansine was delayed and then reduced to 80 mg/m^2, and the patient recovered within 3 weeks. Another patient receiving the 120 mg/m^2 dose had grade 4 hemorrhagic erosive colitis and grade 4 neutropenia during cycle 5 and recovered from both events. Another patient treated with tusamitamab ravtansine 100 mg/m^2 experienced grade 3 keratopathy during cycle 12 and recovered within 1 week.

Nine patients (29.0%) experienced at least one treatment-related corneal TEAE (one of six treated with tusamitamab ravtansine 100 mg/m^2, six of nine treated with 120 mg/m^2, and two of three treated with 150 mg/m^2), including six with grade $\geq$3 corneal TEAEs. Six of these nine patients experienced a first occurrence of a corneal TEAE during the second cycle of treatment with tusamitamab ravtansine 120 mg/m^2 ($n = 4$) and 150 mg/m^2 ($n = 2$), two patients during the fourth cycle of treatment with 120 mg/m^2, and one patient during the 12th cycle of treatment with 100 mg/m^2. Most of these events (in eight of nine patients overall and all six with grade $\geq$3 TEAEs) were described as keratopathy. One patient experienced keratitis and one patient experienced grade $\geq$3 punctate keratitis.

Among the nine patients with corneal events, four had received primary prophylaxis, including two of the three patients treated with 120 mg/m^2 who met the criteria for a DLT. The dose of tusamitamab ravtansine was modified in seven patients after the onset of a corneal event (six dose reductions and cycle delays, and three cycle delays; some patients experienced several episodes) and was permanently discontinued in one patient.

Table 3. Treatment-emergent adverse events (all grades) occurring in ≥10% of patients by dose level and overall (safety population)

Event	Dose of tusamitamab ravtansine (mg/m^2) administered Q2W								All patients (*N* = 31)
	5 ($n = 2$)	10 ($n = 4$)	20 ($n = 1$)	40 ($n = 3$)	80 ($n = 3$)	100 ($n = 6$)	120 ($n = 9$)	150 ($n = 3$)	
Asthenia	0	1	1	0	0	2	3	1	8 (25.8%)
Decreased appetite	1	0	0	2	0	2	2	1	8 (25.8%)
Keratopathy	0	0	0	0	0	1	5	2	8 (25.8%)
Nausea	1	0	0	2	0	1	3	1	8 (25.8%)
Diarrhea	0	0	1	1	0	2	3	0	7 (22.6%)
Constipation	0	0	0	2	0	1	3	1	7 (22.6%)
Fatigue	0	0	0	1	1	1	2	1	6 (19.4%)
Abdominal pain	0	0	0	1	0	2	2	0	5 (16.1%)
Paresthesia	0	0	0	1	0	2	0	1	4 (12.9%)
Dry eye	0	0	0	1	0	1	1	1	4 (12.9%)
Vision blurred	0	0	0	1	0	1	1	1	4 (12.9%)
Cough	0	0	0	0	1	1	1	1	4 (12.9%)

Q2W, once every two weeks.

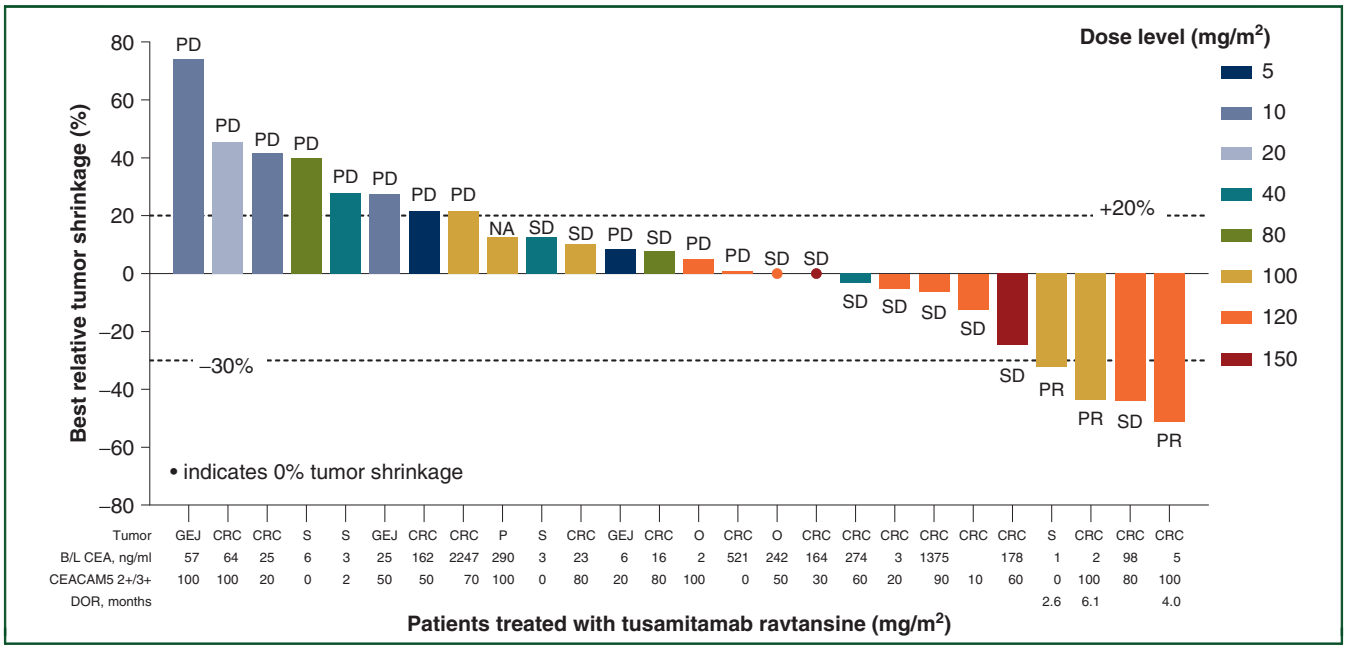

Figure 2. Best overall response according to dose level.

Best relative tumor shrinkage is not calculated for patients without measurable disease at baseline or without post-baseline tumor assessment. Confirmation of response is required [i.e. a second examination done at least 4 weeks apart (i.e. ≥28 days) in order to be documented as a confirmed response].

CEA, carcinoembryonic antigen; CEACAM5; carcinoembryonic antigen-related cell adhesion molecule 5; CRC, colorectal cancer; DOR, duration of response; GEJ, gastroesophageal junction; NA, not assessable (this patient had one post-baseline tumor assessment done 27 days after cycle 1 day 1, before the required 35 days); O, other; P, pancreas; PD, documented progressive disease; PR, confirmed partial response; S, stomach; SD, stable disease.

Eight of nine patients with corneal TEAEs recovered. If a patient had several events, only the maximum recovery time was considered when calculating the median time to recovery, which was 8 days ($n = 1$) at 100 mg/m^2, 26 days (range 8-100, $n = 5$) at 120 mg/m^2, and 59 days (47-71; $n = 2$) at 150 mg/m^2. One patient with grade 2 keratitis had not recovered at the time of the database lock, because this patient died due to disease progression on day 86, at which time the corneal event was considered to be stable.

In addition, eight patients (25.8%), five of whom had a history of neuropathy at the time of study entry and two of whom had received prior treatment with anti-tubulin drugs, experienced peripheral neuropathy events, defined as standardized Medical Dictionary for Regulatory Activities (MedDRA) queries (all grade <3). Six of these eight patients reported peripheral neuropathy at DLs of 100 mg/m^2 ($n = 3$), 120 mg/m^2 ($n = 1$), and 150 mg/m^2 ($n = 2$). Only one patient treated at the MTD who presented with neuropathy (grade 1) had no history of neuropathy nor prior anti-tubulin therapy.

Thrombocytopenia was the most frequently reported laboratory abnormality. The overall incidence of thrombocytopenia (any grade) was 51.6% (16/31). Thirteen patients had grade 1 thrombocytopenia, two had grade 2, and one had grade 4 (unrelated to study treatment). The latter episode occurred at a DL of 100 mg/m^2.

Six deaths occurred during the study. Five were attributed to disease progression and one death not related to disease progression occurred 3 months after treatment was stopped.

Antitumor activity

Of the 31 patients who received tusamitamab ravtansine, 28 (90.3%) permanently discontinued treatment because of disease progression. Across all DLs and tumor types, 29 patients were assessable for tumor response (Figure 2). Three patients (9.7%) had objective responses [all confirmed partial responses (PRs) with durations of 2.6, 6.1, and 4.0 months]; 11 patients (35.5%) had stable disease, and 13 patients (41.9%) had progressive disease. The remaining two patients were classified as non-complete response/non-progressive disease. Among the three patients with objective responses, membrane CEACAM5 expression was graded as ≥2+ in 100% of the tumor cells in two patients, both of whom had colorectal cancer (one had a *KRASG12V* mutation), whereas the third patient had stomach cancer with no reported CEACAM5 expression from an archival sample that only had a limited amount of tumor tissue.

Objective responses were achieved in two of six patients (33.3%) at a DL of 100 mg/m^2, and in one of nine patients (11.1%) at 120 mg/m^2 with maximum reduction in RECIST target lesions of 32.3%-51.2% (Figure 2). Of note, two of the three patients with a partial response experienced grade 3 keratopathy, and the proportion of patients experiencing keratopathy, particularly grade 3, increased with higher exposure to tusamitamab ravtansine; however, the one patient with a partial response and no corneal event had a similar exposure level to one of the two patients with partial responses and grade 3 keratopathy (Supplementary

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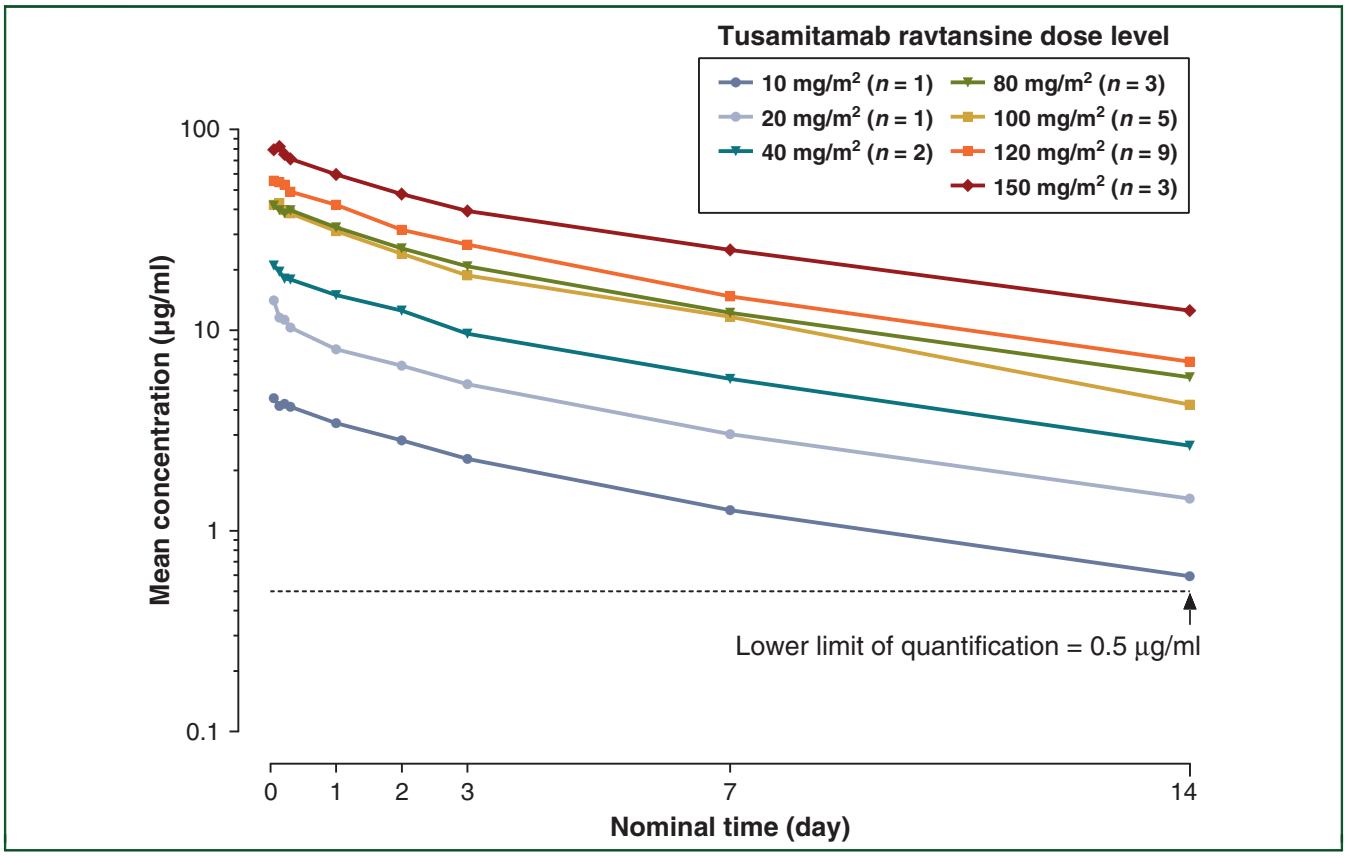

Figure 3. **Mean tusamitamab ravtansine pharmacokinetic profiles during cycle 1.**

Figure S2, available at https://doi.org/10.1016/j.annonc.2021.12.012).

Pharmacokinetics

Overall, 24 of the 31 treated patients were included in calculations of descriptive statistics of PK parameters at cycle 1. The maximum plasma concentration (C_{max}) of tusamitamab ravtansine was generally observed at the end of the infusion, after which plasma concentrations decreased in a biphasic manner (Figure 3). Low variability was observed for C_{max} [coefficient of variation (CV) $<$20%] and moderate variability for area under the curve (AUC; CV $\leq$46%). Mean exposure to tusamitamab ravtansine (C_{max} and AUC) increased in a dose-proportional manner over the dose range of 10 to 150 mg/m^2, with an overlap of individual values over the 80 to 120 mg/m^2 dose range (Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2021.12.012). Tusamitamab ravtansine clearance and terminal elimination half-life were $\sim$0.7 l/day and 6 days, respectively. Clearance was low and roughly constant across DLs, indicating no target-mediated drug disposition over the dose range tested.

Immunogenicity

All 31 treated patients were included in the immunogenicity-assessable population. Five patients (16.1%) had at least one positive sample containing ATAs, one patient each at 20, 80, and 120 mg/m^2 and two patients at 150 mg/m^2. The first positive sample was observed after 2 to 22 weeks of treatment.

DISCUSSION

Tusamitamab ravtansine is generally well tolerated over the dose range of 5 to 100 mg/m^2, and the DLT is dose-related reversible keratopathy. On slit-lamp examination, the appearance of keratopathy was reminiscent of Meesman or Cogan non-inflammatory inherited corneal dystrophies[11,12] (Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2021.12.012). No corneal AEs occurred during the DLT evaluation period in six participants treated with 100 mg/m^2, although one patient did experience grade 3 keratopathy during cycle 12. The incidence of keratopathy was greatest at doses $>$100 mg/m^2 and met the criteria for a DLT in three of eight patients at a DL of 120 mg/m^2 and in two of three patients at a DL of 150 mg/m^2. On this basis, the MTD was determined to be 100 mg/m^2.

Corneal toxicity has been reported in numerous studies involving ADCs with DM4 and other anti-tubulin payloads.[13] The most plausible explanation for such an effect in epithelial tissue that is renewed at a high rate may be non-specific internalization of the ADC in corneal epithelial cells via micropinocytosis followed by DM4-mediated toxicity.[14]

Prophylactic measures were implemented during the trial to prevent keratotoxicity. Patients were pretreated with topical ocular vasoconstrictors and corticosteroids, applied cold masks or pads during the infusion, and were encouraged

to use ocular lubricants. Overall, 9 of 31 patients received prophylaxis for keratotoxicity, including all of those treated with 100 mg/m^2 and three of nine treated with 120 mg/m^2. Topical corticosteroids have been used to manage corneal AEs associated with other ADCs, and when used prophylactically were associated with a decreased incidence of the AE.[15-17] However, the efficacy of these measures is unclear, given that implementation of primary prophylaxis did not allow re-escalation of the dose beyond 100 mg/m^2. No primary prophylactic treatments other than artificial tears and/or hyaluronic acid ophthalmic gel and prohibition of contact lenses are recommended in ongoing trials of tusamitamab ravtansine. Patients should be followed with regular ocular examinations carried out by an ophthalmologist, and corticosteroid-containing ocular drugs are recommended for the management of keratopathy/keratitis should ocular symptoms occur.

With the exception of keratopathy, the incidence of TEAEs potentially associated with a DM4-loaded ADC or CEACAM5-mediated effects was low. One histologically confirmed case of grade 4 colitis occurred at a DL of 120 mg/m^2 with lesions similar to those seen in animal toxicology studies. The frequency and severity of TEAEs were generally similar across the eight DLs evaluated with the exception of corneal toxicity. Excluding keratopathy, the most frequent TEAEs were predominantly low-grade asthenia and fatigue, decreased appetite, and nausea.

The incidence and severity of hematologic toxicity in this study was lower than that generally observed with standard anti-tubulin treatment, such as docetaxel.[18]

The low rate of ATAs observed in this study is consistent with that expected for a humanized monoclonal antibody.

Objective tumor responses were observed in three patients. All patients in whom a partial response was observed and 8 of 11 patients with stable disease received tusamitamab ravtansine at DL $\geq$100 mg/m^2.

The population included in the present study was enriched with, but not restricted to, patients with tumor types known to express CEACAM5. Confirmation of tumor CEACAM5 expression was done retrospectively by a validated assay on archival tissue in a central laboratory. As a result of this sampling methodology, a wide range of CEACAM5 expression was documented. Strong CEACAM5 expression (100%, with an intensity $\geq$2+) was documented in archival tumor tissue samples for the two patients with colorectal cancer who experienced PR. One of these patients also had a *KRASG12V* mutation indicating that CEACAM5 expression and response to tusamitamab ravtansine may be observed irrespective of the *KRAS* mutation status. No tumor CEACAM5 expression could be documented for the third patient with gastric adenocarcinoma who experienced a PR; however, the tumor sample used to evaluate CEACAM5 expression by IHC was described as containing mainly normal stomach lining with limited tumor content. Of note, our internal investigations have confirmed that CEACAM5 expression in human gastric cancers may be found in the same tumor specimen with high intensity or completely lacking depending on the area of observation (Retrospective clinical testing of CEACAM5 in patient samples from the TED13751 / Discovery Life Sciences / 2021-04-30; Sanofi data on file). This highlights the importance of sample quality, especially in the context of potential heterogeneity in target expression that is often documented in this tumor type.

Tusamitamab ravtansine is the first CEACAM5—maytansinoid ADC to be evaluated in human subjects. An ADC that targeted CEACAM5 that is coupled to the active metabolite of irinotecan (SN38, a topoisomerase inhibitor) via a pH-sensitive linker was previously evaluated in patients with metastatic colorectal cancer.[19,20] Common AEs of this compound (labetuzumab govitecan) were neutropenia and diarrhea, consistent with the SN38 payload. Development of labetuzumab govitecan appears to have been halted.[20]

The single-dose pharmacokinetics of tusamitamab ravtansine had low to moderate variability. The low clearance of 0.7 l/day was consistent with that predicted from allometric scaling of monkey PK data.[6] Mean exposure to tusamitamab ravtansine increased in a dose-proportional manner over the dose range studied with some overlap of individual values over the 80- to 120-mg/m^2 range. Although the proportion of patients experiencing keratopathy, particularly grade 3, increased with higher exposure to tusamitamab ravtansine, the limited number of responders in a heterogeneous patient population does not allow any conclusions to be drawn about a relationship between treatment response and keratopathy (Supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2021.12.012).

Tusamitamab ravtansine is currently being evaluated in patients with advanced CEACAM5-positive non-squamous non-small-cell lung cancer. Although this population was not treated in this dose-finding study, strong CEACAM5 tumor expression occurs at relevant rates in this tumor type for which anti-tubulin agents have been used for approximately two decades. Ongoing trials include a phase II study in which tusamitamab ravtansine is combined with pembrolizumab (NCT04524689), a phase II study in combination with ramucirumab (NCT04394624), and a phase III trial that compares tusamitamab ravtansine with docetaxel (NCT04154956).

In conclusion, tusamitamab ravtansine had a favorable safety profile in this phase I clinical trial. The DLT was determined to be reversible and manageable dose-related keratopathy. The MTD was determined to be 100 mg/m^2.

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DATA SHARING

Qualified researchers may request access to patient-level data and related documents (including, e.g. the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and dataset specifications). Patient-level data will be anonymized, and study documents will be redacted to protect the privacy of trial participants. Further details on Sanofi's data-sharing criteria, eligible studies, and process for requesting access can be found at https://www.clinicalstudydatarequest.com.

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