ORIGINAL ARTICLE

Evaluation of the Safety, Pharmacokinetics, and Antitumor Activity of Tusamitamab Ravtansine in Patients With Nonsquamous NSCLC With High or Moderate Expression of Carcinoembryonic Antigen-Related Cell Adhesion Molecule 5

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ABSTRACT

Introduction: Tusamitamab ravtansine is an antibody-drug conjugate targeting cells expressing carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5) with a maytansinoid payload, DM4. This phase 1b dose-expansion study (NCT02187848) evaluated its safety, pharmacokinetics, and preliminary antitumor activity in patients with nonsquamous NSCLC (NSq NSCLC).

Methods: Patients aged above or equal to 18 years with advanced or metastatic NSq NSCLC, life expectancy more

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than or equal to 12 weeks, and high (≥2+ intensity in ≥50% of tumor cells) or moderate (≥2+ intensity in 1%–49% of tumor cells) CEACAM5 expression (assessed by immunohistochemistry) received intravenous tusamitamab ravtansine 100 mg/m^2 every 2 weeks.

Results: A total of 64 patients with high and 28 with moderate CEACAM5 expression received a median of 8.0 (1–69) and 4.5 (1–38) treatment cycles, respectively. High expressors had 13 confirmed partial responses and 28 stable diseases (objective response rate, 20.3%; 95% confidence interval [CI]: 12.3%–31.7%, $p < 0.0001$); median duration of response was 6.7 months, and median time to progression was 3.7 months (95% CI: 2.7–5.1 mo). Moderate expressors had two confirmed partial responses (objective response rate, 7.1%; 95% CI: 2.0%–22.7%, $p = 0.4117$) and 15 stable diseases. Treatment-emergent adverse events (AEs) occurred in 78.3% of patients (72/92), 37.0% (34/92) of patients required dose modifications, and 5.4% (5/92) discontinued treatment. The most common treatment-emergent AEs included asthenia (37.0%), keratitis (29.3%), and dyspnea (23.9%). Corneal AEs occurred in 38.0% (35/92), typically grade 1/2, reversible, and manageable by dose modifications.

Conclusions: Tusamitamab ravtansine demonstrated a favorable safety profile, objective responses, and antitumor activity in patients with high CEACAM5-expressing NSq NSCLC.

Keywords: Antibody-drug conjugate; Carcinoembryonic antigen-related cell adhesion molecule 5; Non–small cell lung cancer; Phase 1 study; Tusamitamab ravtansine

Introduction

Lung cancer is the leading cause of cancer mortality worldwide.[1] NSCLC accounts for approximately 85% of all lung cancers.[2] In the United States, the 3-year relative survival rate for patients diagnosed with having NSCLC in 2004 to 2006 versus 2016 to 2018 increased from 25% to 38%.[3] Despite this improvement, median overall survival in real-world cohorts of patients with advanced metastatic NSCLC ranges from 9.7 to 12.3 months.[4–6] Thus, there is an ongoing need to develop novel agents for the treatment of NSCLC.

Antibody-drug conjugates (ADCs) are a promising therapeutic approach to improve outcomes in patients with advanced metastatic cancer.[7] The ideal target for an ADC is a cell-surface protein expressed only on tumor cells.[7] One such candidate is carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5), a cell-surface glycoprotein minimally expressed in normal epithelial tissues but highly expressed in several tumors.[8,9] Expression of CEACAM5 is elevated in human NSCLC tissue and may correlate with clinical stage and histologic grade.[9,10] CEACAM5 expression measured by different methods has been reported to be associated with worse survival and all-cause mortality in patients with NSCLC and to be correlated with an imminent diagnosis of lung cancer.[11–13]

Tusamitamab ravtansine (SAR408701) is an ADC that comprises a humanized anti-CEACAM5 antibody joined by a cleavable N-succinimidyl 4-(2-pyridyldithio)butyrate linker to a cytotoxic maytansinoid payload (DM4) with a mean drug-to-antibody ratio of 3.8.[14] DM4 and its S-methylated metabolite (Me-DM4) are cell membrane-permeable inhibitors of microtubule assembly leading to apoptosis in both target and, through a "bystander effect," neighboring cells.[9,14–16]

Tusamitamab ravtansine exhibited antitumor activity in vitro and in patient-derived xenograft models,[9] from which a pharmacokinetic-pharmacodynamic model[14] was derived to guide dosing in the first-in-human clinical trial.[17]

The safety, dose-limiting toxicity (DLT), and maximum tolerated dose of tusamitamab ravtansine were determined in a first-in-human phase 1/1b study in patients with advanced solid tumors (ClinicalTrials.gov NCT02187848).[17,18] In the main dose-escalation part, the DLT was dose-related reversible keratopathy, and the maximum tolerated dose was 100 mg/m^2 every 2 weeks.[17] Here, we present the results from two dose-expansion cohorts in the same phase 1/1b study to describe the safety, pharmacokinetics (PK), and antitumor activity of tusamitamab ravtansine 100 mg/m^2 every 2 weeks in patients with nonsquamous (NSq) NSCLC.

Methods

Study Design

This study in patients with solid tumors comprised a phase 1 dose-escalation part previously reported[17] and a phase 1b dose-expansion part, the NSCLC cohorts of which are reported here (Fig. 1). The study was conducted in accordance with the Declaration of Helsinki, International Conference on Harmonisation, and Good Clinical Practice guidelines. The study was approved by the presiding ethics committee at each site, and all patients provided written informed consent before participating in the trial.

Patients

Patients eligible for the NSq NSCLC dose-expansion part of the trial were at least 18 years of age, had an

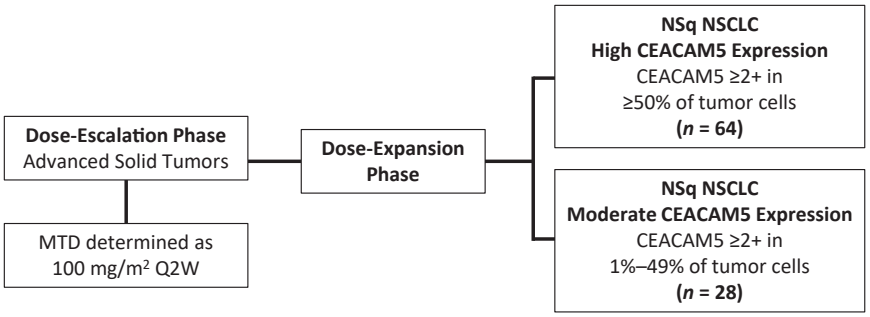

Figure 1. Study design. CEACAM5, carcinoembryonic antigen-related cell adhesion molecule 5; MTD, maximum tolerated dose; NSq NSCLC, nonsquamous NSCLC; Q2W, every 2 weeks.

Eastern Cooperative Oncology Group performance status of 0 or 1, and had locally advanced or metastatic NSq NSCLC for which no standard alternative therapy was available. Patients were required to have at least one measurable lesion by Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1[19] and either high ($\geq$2+ intensity in $\geq$50% of tumor cells) or moderate ($\geq$2+ intensity in 1%–49% of tumor cells) expression of CEACAM5. Cell membrane expression of CEACAM5 was determined prospectively in the most recent formalin-fixed, paraffin-embedded archival tumor tissue sample by immunohistochemistry (IHC) at local or central laboratories (Supplementary Materials) using a proprietary murine CEACAM5-specific antibody (CEACAM5 IHC 769 clone).[9]

Patients were excluded if they had poor organ function, low bone marrow reserve, known or symptomatic brain metastasis (other than totally resected or previously irradiated and non-progressive/relapsing), an expected life expectancy less than 12 weeks, a history of or unresolved corneal disorders, or if they had previously received CEACAM5-targeted or maytansinoid-based therapy.

Treatment

Intravenous tusamitamab ravtansine 100 mg/m^2 every 2 weeks was infused at 2.5 mg/min for 30 minutes and then at 5 mg/min. Treatment was continued until disease progression, unacceptable toxicity, or willingness to stop. All patients were encouraged to use lubricating eye drops 3 to 6 times a day; depending on the date of study enrollment, patients received either right-eye only primary corneal prophylaxis or bilateral secondary corneal prophylaxis (Supplementary Materials).

End Points

The primary end point was the objective response rate (ORR), defined as the percentage of patients with a confirmed objective response (OR) of complete response (CR) or partial response (PR) by RECIST version 1.1 criteria.[19] Secondary variables included duration of response (DOR), time to tumor progression (TTP), safety, and PK of tusamitamab ravtansine, DM4, and its metabolite Me-DM4.

Assessments

Tumor assessments were performed at least every 4 cycles, and tumor growth rate was assessed using RECIST version 1.1.[20] Confirmed CR or PR required confirmation at least after 4 weeks. Baseline patient mutation data were collected when available.

Safety was assessed by physical examination, laboratory tests, and adverse event (AE) reports. AEs were graded according to the National Cancer Institute Common Terminology for Adverse Events (version 4.03) and coded using the Medical Dictionary for Regulatory Activities (version 23.1). Ophthalmologic assessments are described in the Supplementary Materials.

Tusamitamab ravtansine plasma concentrations were determined by a validated immunoassay (lower limit of quantitation [LLOQ] 0.500 μg/mL) that detects ADCs with at least 1 DM4 moiety. Plasma concentrations of DM4 and Me-DM4 were determined by a validated liquid-chromatography–tandem mass spectrometry assay (LC-MS/MS, LLOQ 0.200 ng/mL). Pharmacokinetic parameters were calculated by standard noncompartmental analysis. Immunogenicity assessments are described in the Supplementary Materials.

Data Analysis

The primary efficacy analysis used the all-treated population (patients who received at least one dose of tusamitamab ravtansine) by CEACAM5 expression cohort (high or moderate). DOR was calculated for patients with a confirmed response, and the median TTP was estimated using the Kaplan-Meier method. Tumor shrinkage was evaluated using the response-evaluable population (treated patients with measurable disease at study entry and at least one post-baseline assessable tumor assessment). The PK population comprised

patients with at least one drug concentration measurement after study drug administration.

The ORR and 95% confidence intervals (CIs) were estimated using the Wilson score interval. A binomial test against the null hypothesis (response rate = 5%) was performed using a one-sided test with an alpha level of 0.025.

A post hoc analysis using the Kaplan-Meier method evaluated progression-free survival (PFS).

Results

Of 888 patients with NSq NSCLC who were prescreened for CEACAM5 expression, 172 patients (19.4%) had high CEACAM5 expression and 210 (23.6%) had moderate CEACAM5 expression. From these individuals with NSq NSCLC, 80 patients with high CEACAM5 expression and 44 with moderate CEACAM5 expression were screened, of whom 64 and 28 patients, respectively, were enrolled. The first patients were enrolled on January 2, 2017, and the last patient received cycle 1 on October 8, 2019; the data cutoff date was November 19, 2020. Known or symptomatic brain metastases or leptomeningeal carcinomatosis were the most common reason for exclusion (six and four patients with high and moderate CEACAM5 expression, respectively). At the data cutoff, six patients (9.4%) with high CEACAM5 expression and one patient (3.6%) with moderate CEACAM5 expression remained on treatment.

All patients had metastatic and measurable disease, and most patients had received at least three previous regimens, including previous anti-programmed cell death protein 1/programmed cell death ligand 1 (anti–PD-1/PD-L1) treatment, and had discontinued their most recent regimen because of disease progression (Table 1). Among 64 patients with high CEACAM5 expression, more than half (53.1%) had CEACAM5 intensity more than or equal to 2+ expression in more than or equal to 80% of tumor cells. Among 28 patients with moderate CEACAM5 expression, the percentage of tumor cells with more than or equal to 2+ intensity membrane staining was median 9.5% (range, 1.0%–40.0%).

Limited data were available for molecular alterations at baseline, which were collected as part of patient history; however, among those who were evaluated, the most common molecular alterations involved *KRAS* and *EGFR* (Supplementary Table 1).

The median duration of study treatment at the data cutoff was 3.9 months (range 0.5–35.5 mo) in patients with high CEACAM5 expression and 2.3 months (0.5–20.9 mo) in patients with moderate CEACAM5 expression. The median number of treatment cycles was 8.0 (range 1.0–69.0) and 4.5 (1.0–38.0) per patient, respectively. In patients with high CEACAM5 expression, cycle delays, dose reduction, and dose interruptions occurred in 45.3%, 12.5%, and 1.6% of patients, respectively; corresponding values in patients with moderate CEACAM5 expression were 35.7%, 10.7%, and 0%. Reasons for discontinuation for patients with high and moderate CEACAM5 expression, respectively, included disease progression (54 [84.4%] and 23 [82.1%] patients), AEs (3 [4.7%]

Table 1. Baseline Demographics and Patient Characteristics

Parameters	High CEACAM5 Expression $n = 64$	Moderate CEACAM5 Expression $n = 28$
Age, y, median (range)	61.5 (41-91)	64.5 (31-73)
Age group, y, *n* (%)		
<65	39 (60.9)	14 (50.0)
≥65 to <75	17 (26.6)	14 (50.0)
≥75	8 (12.5)	0
Female, *n* (%)	27 (42.2)	18 (64.3)
Race, *n* (%)		
White	52 (81.3)	25 (89.3)
Asian	12 (18.8)	3 (10.7)
ECOG PS, *n* (%)		
0	19 (29.7)	7 (25.0)
1	45 (70.3)	20 (71.4)
2	0	0
3	0	1 (3.6%)
Organs involved (≥20% in either group),[a] *n* (%)		
Lung	57 (89.1)	24 (85.7)
Lymph node	33 (51.6)	21 (75.0)
Bone	23 (35.9)	7 (25.0)
Pleura	20 (31.3)	5 (17.9)
Liver	17 (26.6)	6 (21.4)
Brain	13 (20.3)	4 (14.3)
Number of prior regimens, median (range)	3 (1-10)	3 (1-8)
Number of prior regimens, *n* (%)		
1	2 (3.1)	1 (3.6)
2	18 (28.1)	9 (32.1)
≥3	44 (68.8)	18 (64.3)
Prior anti-PD-1/PD-L1 treatment, *n* (%)	45 (70.3)	24 (85.7)
Discontinuation of last regimen due to disease progression	51 (79.7)	22 (78.6)
CEACAM5 expression (intensity 2+/3+)[b]		
≥80%	34 (53.1)	–
50% to <80%	30 (46.9)	–
<50%	–	28 (100)
Circulating CEA ≥5 μg/L, *n* (%)	53 (85.5)	23 (82.1)

[a]Organs involved include target or nontarget lesions as defined by Response Evaluation Criteria in Solid Tumours version 1.1 and reported by study investigators at baseline.
[b]CEACAM5 expression was assessed on the most recently available archival tissue sample (Supplementary Materials) and evaluated by local or central laboratory.
CEA, carcinoembryonic antigen; CEACAM5, carcinoembryonic antigen-related cell adhesion molecule 5; ECOG PS, Eastern Cooperative Oncology Group performance status; PD-1/PD-L1, programmed cell death protein 1/programmed cell death ligand 1.

Table 2. Best Overall Response in Patients With NSCLC With High and Moderate CEACAM5 Expression

Parameters, *n* (%)	Patients With High CEACAM5 Expression[a] *n* = 64	Patients With Moderate CEACAM5 Expression[b] *n* = 28
Best overall response		
Complete response (CR)[c]	0	0
Partial response (PR)[c]	13 (20.3)	2 (7.1)
Stable disease (SD)	28 (43.8)	15 (53.6)
Progressive disease (PD)	16 (25.0)	8 (28.6)
Not evaluable[d]	7 (10.9)	3 (10.7)
Disease control rate (CR, PR, and SD)	41 (64.1)	17 (60.7)
Objective response rate (confirmed CR and PR)	13 (20.3)	2 (7.1)
95% CI, %	(12.3-31.7)	(2.0-22.7)
p value[e]	<0.0001	0.4117

[a]Defined as more than or equal to 2+ staining intensity in more than or equal to 50% of the tumor cell population, as assessed by immunohistochemistry.
[b]Defined as more than or equal to 2+ staining intensity in 1% to 49% of the tumor cell population.
[c]Confirmation of response was required (a second examination was performed at least 4 wk apart).
[d]Includes patients with no post-baseline evaluation due to early death or early progression based on symptomatic deterioration.
[e]Binomial test against the null hypothesis of response rate of 5% performed using a one-sided 0.025 alpha level.
CEACAM5, carcinoembryonic antigen-related cell adhesion molecule 5; CI, confidence interval; CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

and 2 [7.1%] patients), and other reasons (1 [1.6%] and 2 [7.1%] patients).

Antitumor Activity

Among 64 patients with high CEACAM5 expression, the best overall responses were confirmed PRs in 13 patients (ORR, 20.3% [95% CI: 12.3%–31.7%]) and stable disease (SD) in 28 patients (43.8%) (Table 2). Among patients with a confirmed OR, the median DOR at the data cutoff was 6.7 months (95% CI: 3.68 to not calculated), and the median TTP was 3.7 months (95% CI: 2.7–5.1 mo) with nine patients censored. Figure 2*A–C* illustrates tumor shrinkage by best overall response over time.

In patients with moderate CEACAM5 expression (n = 28), two had confirmed PR and 15 had SD as best overall response (Table 2; Fig. 2*B*). The confirmed ORR was 7.1% (95% CI: 2.0%–22.7%). The DORs for the two patients with confirmed PR were 3.9 and 18 months at the data cutoff, and the median TTP was 2.8 months (95% CI: 1.7–3.7 mo).

In a post hoc analysis, median PFS was 3.7 months (95% CI: 2.7–5.1) and 2.8 months (95% CI: 1.7–3.7) in patients with high and moderate CEACAM5 expression, respectively (Supplementary Fig. 1).

Among patients with high CEACAM5 expression, a confirmed objective response (OR) was observed in eight of 34 patients (23.5%; 95% CI: 12.4%–40.0%) with CEACAM5 expression in ≥80% of tumor cells, and in five of 30 patients (16.7%; 95% CI: 7.3%–33.6%) with CEACAM5 expression in 50% to <80% of tumor cells. Among patients with high CEACAM5 expression and evaluable tumors, mean (standard deviation) relative change from baseline in the sum of tumor diameters was −13.2% (29.6%) for patients with CEACAM5 intensity ≥2+ in ≥80% of tumor cells (n = 29), and −9.2% (34.3%) for patients with CEACAM5 intensity ≥2+ in 50% to <80% of tumor cells (n = 28; Fig. 2*C*).

Patients with OR are grouped by prognostic factors at baseline in Supplementary Table 2. For patients with high CEACAM5 expression NSCLC treated with tusamitamab ravtansine in this study, a confirmed OR occurred in eight of 45 patients (17.8%, 95% CI: 9.3%–31.3%) with previous anti–PD-1/PD-L1 treatment; five of 19 patients (26.3%, 95% CI: 11.8%–48.8%) without previous anti–PD-1/PD-L1 treatment; six of 39 patients (15.4%; 95% CI: 7.3%–29.7%) who had previously received an anti-tubulin agent; and seven of 25 patients (28.0%; 95% CI: 14.3%–47.6%) who had not received a previous anti-tubulin agent.

In post hoc analyses of response in patients with NSCLC with *EGFR* or *KRAS* alterations, confirmed PRs were observed in one of 11 patients (9.1%, 95% CI: 1.6%–37.7%) with *EGFR* alterations and high CEACAM5 expression, three of 21 patients (14.3%, 95% CI: 5.0%–34.6%) with *KRAS* alterations and high CEACAM5 expression, and two of nine patients (22.2%, 95% CI: 6.3%–54.7%) with *KRAS* alterations and moderate CEACAM5 expression.

Treatment-Emergent Adverse Events

All patients (N = 92) experienced at least one treatment-emergent AE (TEAE), 72 (78.3%) experienced at least one treatment-related AE, and four (4.3%) experienced serious treatment-related AEs (one each of

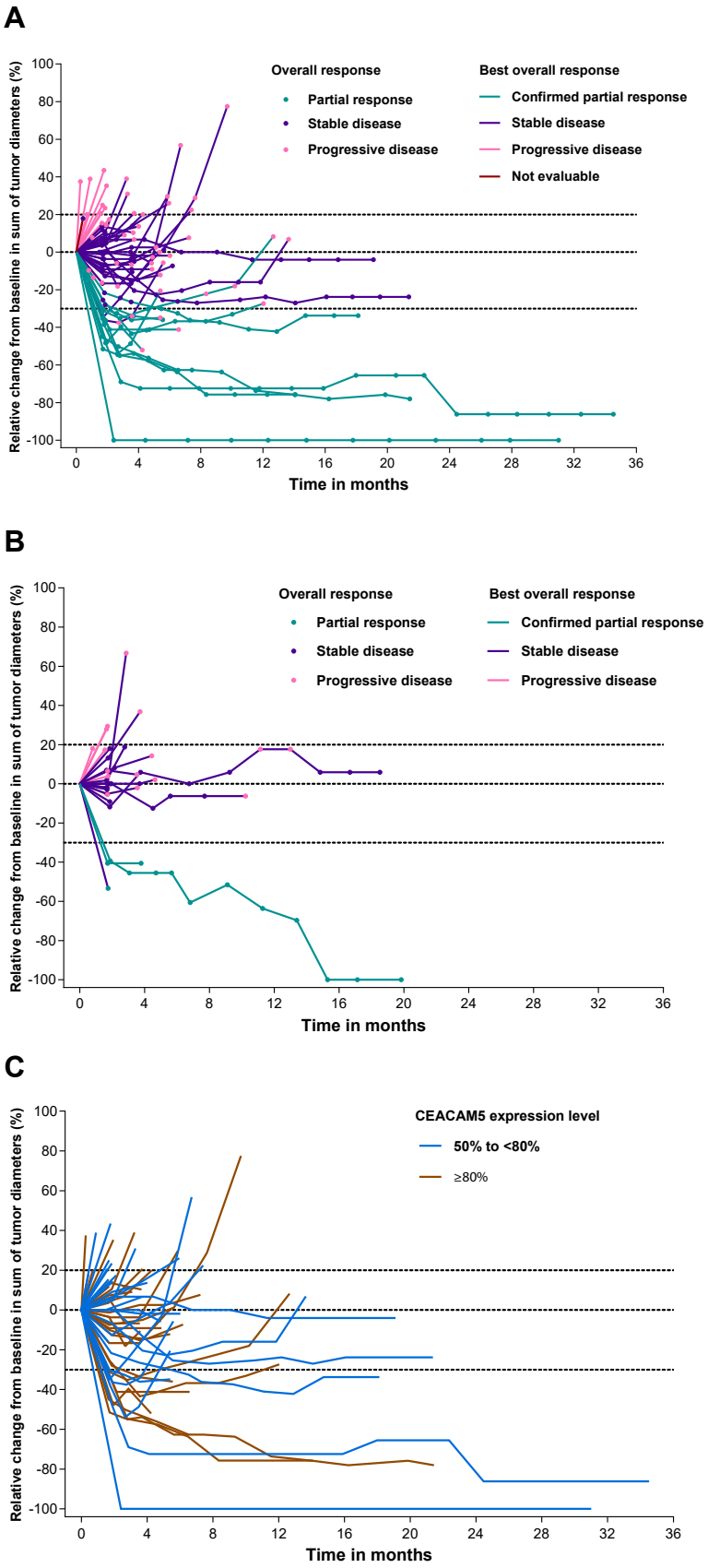

Figure 2. Relative change from baseline in sum of tumor diameters over time in patients with nonsquamous NSCLC who were treated with tusamitamab ravtansine 100 mg/m^2 every 2 weeks and had evaluable responses. (**A, B**) Relative change from

Table 3. Adverse Events

Event	Patients, *n* (%) *N* = 92	
Any TEAE	92 (100)	
TEAE grade ≥3	50 (54.3)	
TEAE grades 3–4	49 (53.3)	
TEAE grade 5	7 (7.6)	
Any serious TEAE	41 (44.6)	
Any treatment-related AE	72 (78.3)	
Treatment-related AE grade ≥3	18 (19.6)	
Treatment-related AE grades 3–4	18 (19.6)	
Treatment-related AE grade 5	0	
Any serious treatment-related AE	4 (4.3)	
Any TEAE leading to dose modification[a]	34 (37.0)	
Any TEAE leading to permanent treatment discontinuation	5 (5.4)	
TEAEs occurring in ≥10% of patients	All grades	Grade ≥3
Asthenia	34 (37.0)	4 (4.3)
Keratitis	27 (29.3)	10 (10.9)
Dyspnea	22 (23.9)	11 (12.0)
Decreased appetite	21 (22.8)	0
Diarrhea	21 (22.8)	1 (1.1)
Keratopathy	14 (15.2)	2 (2.2)
Cough	14 (15.2)	0
Nausea	13 (14.1)	1 (1.1)
Arthralgia	13 (14.1)	0
Peripheral sensory neuropathy	12 (13.0)	0
Constipation	10 (10.9)	0
Hematological TEAEs[b]		
Anemia	3 (3.3)	2 (2.2)
Lymphopenia	1 (1.1)	1 (1.1)
Neutropenia	1 (1.1)	0
Neutrophil count decreased	1 (1.1)	0
Platelet count decreased	1 (1.1)	0

[a]Dose reductions and/or interruptions and/or delayed treatment cycles.
[b]Includes all blood and lymphatic system disorders (system organ class) and all investigations related to blood/lymphatic systems that were recorded by the investigator as a TEAE (defined as laboratory abnormalities considered to be medically relevant).
AE, adverse event; TEAE, treatment-emergent adverse event.

peripheral sensory neuropathy, peripheral sensorimotor neuropathy, transient ischemic attack, and hypokalemia) (Table 3). In addition, 34 patients (37.0%) experienced TEAEs that required dose modifications and five patients (5.4%) experienced TEAEs that led to permanent discontinuation of tusamitamab ravtansine. Furthermore, 11 patients experienced TEAEs that resulted in death, none of which were related to the study treatment. The most common TEAEs were asthenia (37.0%), keratitis (29.3%), dyspnea (23.9%), decreased appetite (22.8%), and diarrhea (22.8%). No alopecia was reported.

There were 35 patients (38.0%) who experienced at least one corneal TEAE (11 experienced at least one grade 3 event). These included 27 patients (29.3%) with keratitis (10 with grade 3 events), 14 (15.2%) with keratopathy (two with grade 3 events), and one (1.1%) with superior limbic keratoconjunctivitis. No grade 4 (e.g., blindness, perforation) or serious corneal TEAEs occurred. All corneal TEAEs were treatment related. The first occurrence of corneal TEAEs was at cycle 2 in 11 patients, cycle 3 in five patients, and later in 19 patients. Among 35 patients with corneal TEAEs, dose modifications were implemented in 25; however, no patient required permanent discontinuation of the study drug. At the data cutoff, 25 patients had recovered, nine had not, and the outcome of one patient was unknown. No patient had a corneal event that resulted in permanent sequalae. The median time to recovery was 22 days (range, 8–264 d) in 17 patients with high CEACAM5 expression and 16.5 days (range, 8–30 d) in eight patients with moderate CEACAM5 expression. Mean exposure to tusamitamab ravtansine during cycle 1 was higher in patients with corneal AEs than that in those without corneal AEs (Supplementary Fig. 2).

Approximately half (7/13; 53.8%) of the patients with high CEACAM5 expression and a PR had a corneal event. Among patients with high CEACAM5 and corneal AEs, a PR was observed in five of 17 patients (29.4%; 95% CI: 13.3%–53.1%) with grade 1 to 2 corneal events and in two of nine patients (22.2%; 95% CI: 6.3%–54.7%) with grade 3 corneal events. In contrast, six of 38 patients (15.8%; 95% CI: 7.4%–30.4%) with high CEACAM5 expression and no corneal event had a PR. Both patients with moderate CEACAM5 expression and a PR had a corneal event (one each grade 2 and grade 3).

Pharmacokinetics

Maximum plasma concentrations of tusamitamab ravtansine were generally observed close to the end of the infusion, whereas those of DM4 and Me-DM4

baseline in sum of tumor diameters in patients with (**A**) high CEACAM5 expression ($n = 57$), which was defined as more than or equal to 2+ intensity in more than or equal to 50% of the tumor cell population, or (**B**) moderate CEACAM5 expression ($n = 25$), which was defined as more than or equal to 2+ intensity in 1% to 49% of the tumor cell population, by best overall response (confirmed PR, teal; SD, purple; PD, pink). (**C**) Relative change from baseline in sum of tumor diameters in patients with high CEACAM5 expression by subgroups of CEACAM5 expression more than or equal to 2+ in more than or equal to 80% of tumor cells ($n = 29$) or in 50% to less than 80% of tumor cells ($n = 28$). CEACAM5 expression was determined by immunohistochemical analysis of tumor tissue (primarily archival). Dotted lines indicate cutoffs for PD (≥20% increase in the sum of target lesion tumor diameter), SD (+20% to −30%), and PR (≥30% decrease in the sum of target lesion tumor diameters). CEACAM5, carcinoembryonic antigen-related cell adhesion molecule 5; PD, progressive disease; PR, partial response; Q2W, every 2 weeks; SD, stable disease.

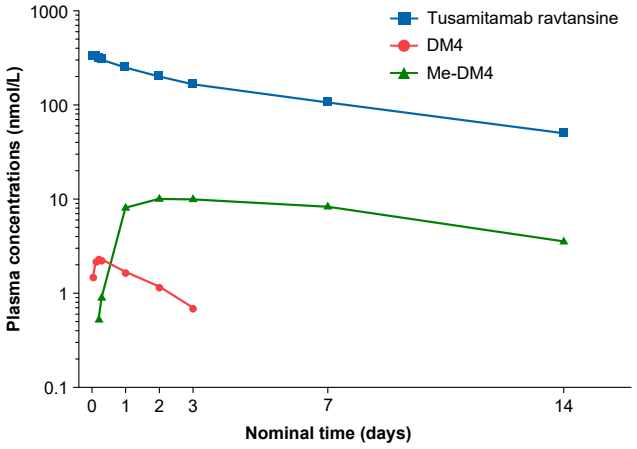

Figure 3. Mean plasma concentration of tusamitamab ravtansine, its payload DM4, and its metabolite Me-DM4 at cycle 1 in patients with high CEACAM5 expression. CEACAM5, carcinoembryonic antigen-related cell adhesion molecule 5; DM4, maytansine derivative; Me-DM4, methylated-DM4.

occurred after (approximately 5 and 48 h, respectively) (Fig. 3 and Supplementary Tables 3 and 4). Steady state was reached by cycle 4. The mean terminal elimination half-life for tusamitamab ravtansine was approximately 6 days (Supplementary Table 3). There were no obvious differences in exposure to tusamitamab ravtansine, DM4, or Me-DM4 between patients with high or moderate CEACAM5 expression (Supplementary Tables 3 and 4), consistent with previously reported population PK analyses that did not identify CEACAM5 as a covariate affecting PK.[21]

Immunogenicity

Treatment-induced antitherapeutic antibodies were observed in seven patients with high CEACAM5 expression and one patient with moderate CEACAM5 expression.

Patients Treated Long Term

As of April 2022, 11 of 92 patients with high ($n = 9$) or moderate ($n = 2$) CEACAM5 expression had received tusamitamab ravtansine for at least 12 months, of whom seven had a confirmed PR and four had SD as best overall response (Supplementary Table 5 and Supplementary Fig. 3). The patients with a confirmed PR ($n = 7$) had a median DOR of 23.9 (range 8.5–44.9) months (Supplementary Fig. 4). No clinically meaningful new or unexpected safety signals were observed as of April 2022 compared with the safety profile established for the overall cohorts ($n = 92$) at the overall study cutoff (November 2020) (Supplementary Table 6).

Corneal TEAEs were observed in eight of 11 patients who received tusamitamab ravtansine for at least 12 months, four of whom experienced grade 3 events; the first occurrence of any corneal TEAE ranged from cycle 2 to 6. Among patients treated for at least 12 months, corneal TEAEs were managed by treatment modifications in seven patients; no corneal TEAE led to permanent treatment discontinuation.

Discussion

The results of this study demonstrated that tusamitamab ravtansine 100 mg/m^2 every 2 weeks in patients with NSq NSCLC had a favorable safety profile with antitumor activity and manageable corneal TEAEs. Furthermore, six of 15 patients with a confirmed PR maintained it for at least 12 months, and of patients treated for at least 12 months, the median DOR was almost 2 years, suggesting that the therapeutic response was durable and sustained in this heavily pretreated population.

The AE profile of patients with NSq NSCLC in this study was generally consistent with observations in previously described cohorts from this phase 1/1b study.[17,18] Importantly, hematological TEAEs were not a prominent aspect of the AE profile.

Corneal events were established as the main DLT of tusamitamab ravtansine in the phase 1 dose-escalation part of this study and were confirmed in subsequent dose-escalation cohorts that received alternative dosing regimens of tusamitamab ravtansine.[17,18] Corneal events in the dose-escalation cohorts were generally keratopathy, managed by dose modifications (cycle delays and/or dose reductions), and were reversible after discontinuation of tusamitamab ravtansine; none resulted in permanent sequelae.[17,18] Primary prophylaxis with a topical ocular vasoconstrictor and corticosteroid was evaluated in a pool of patients from multiple cohorts in this phase 1/1b study but did not seem to mitigate corneal events.[22] Hence, primary prophylaxis was not offered in subsequent clinical trials of tusamitamab ravtansine.[17] Rather, secondary prophylaxis was to be considered when recommended by an ophthalmologist.

In the NSq NSCLC cohorts in this study, 38.0% of patients experienced at least one corneal TEAE, including keratitis, keratopathy, and superior limbic keratoconjunctivitis. Approximately half of these events occurred for the first time during the first four treatment cycles. Consistent with previous findings, all corneal events were nonserious and were typically manageable by dose modification (dose reductions and/or cycle delays).

Corneal AEs have been reported previously for ADCs containing DM4 and other anti-tubulin payloads.[23,24] Although the mechanism of ADC-related ocular toxicity is not completely understood, one possible mechanism for corneal TEAEs involves nonspecific internalization of the ADC into corneal epithelial cells by macropinocytosis

or micropinocytosis, with subsequent DM4-mediated cytotoxicity.[24,25]

In this study, seven patients experienced grade 5 TEAEs, but no grade 5 TRAEs were reported, indicating that fatal events were not treatment related. These events were likely due to disease progression or other underlying factors.

Tusamitamab ravtansine 100 mg/m^2 every 2 weeks demonstrated antitumor activity in patients with NSq NSCLC and high CEACAM5 expression but seemed to be less effective in patients with moderate CEACAM5 expression. Among patients with moderate expression, the confirmed ORR was 7.1%, which was not significantly different from that of the null hypothesis (5%). The relative effectiveness of tusamitamab ravtansine in patients with high versus moderate CEACAM5 expression is consistent with its CEACAM5-directed design.

CEACAM5 expression status was determined prospectively by either local or central immunohistochemical analysis of tumor tissue, primarily on archival samples. However, IHC tests have some limitations. Expression of CEACAM5 in the archival sample may not reflect CEACAM5 expression at study initiation. Furthermore, CEACAM5 expression assessed in an archival sample from one biopsy location may not reflect that of the advanced or metastatic disease. Further investigations are needed to assess potential changes in CEACAM5 expression during the course of the disease.

Overall, approximately 20% of patients in this phase 1/1b study who were prescreened for CEACAM5 expression had high CEACAM5 expression. The prevalence of high CEACAM5 expression in this study is consistent with the approximately 25% of patients with NSCLC having high CEACAM5 expression in a recently reported single-center study and the approximately 28% of tumor specimens with strong-to-moderate IHC staining in lung adenocarcinoma human tumor tissues.[9,26] Further study is required to better define the subsets of patients with NSCLC who stand to benefit from tusamitamab ravtansine.

In a post hoc analysis, we analyzed the potential relationship between efficacy and toxicity (i.e., corneal AEs), which has been reported for diverse anticancer therapies.[27] We observed that among patients in the high CEACAM5 expression group, the proportion of patients with a confirmed PR was greater for those with a corneal AE than that in those without (26.9% versus 15.8%). These findings are consistent with the observed positive correlation between mean exposure to tusamitamab ravtansine during treatment cycle 1 and corneal AEs in this study and with results from the dose-escalation part of the study.[17]

Additional analyses of other characteristics of patients with NSCLC who responded to tusamitamab ravtansine, including previous treatment with an anti-tubulin agent and molecular alterations present at baseline, did not reveal any obvious differences in confirmed ORR compared with that in nonresponders. Notably, among patients with high CEACAM5 expression, those without previous anti-tubulin treatment had a greater confirmed ORR than those with previous anti-tubulin treatment (28.0% versus 15.4%).

No patients in this trial experienced a CR; however, achievement of a PR is likely clinically meaningful considering that the participants had advanced or metastatic disease and were heavily pretreated (at least two previous lines of chemotherapy). In this context, patients with high CEACAM5 expression who had a confirmed PR ($n = 13$) or SD ($n = 28$) are notable.

On the basis of the results of this phase 1/1b study, the efficacy and safety of tusamitamab ravtansine were explored in patients with NSCLC and CEACAM5 expression in subsequent studies. The phase 3 CARMEN-LC03 study (NCT04154956) assessed the PFS and overall survival of patients with high CEACAM5 expression who receive tusamitamab ravtansine monotherapy every 2 weeks versus docetaxel. The phase 2 studies CARMEN-LC04 (NCT04394624), in patients with high CEACAM5 expression, and CARMEN-LC05 (NCT04524689), in patients with moderate and high CEACAM5 expression, aimed to explore tusamitamab ravtansine in combination regimens with ramucirumab or pembrolizumab, respectively.

Our study has few limitations. This was a phase 1 study with relatively small number of patients and heavily pretreated participants. The study was not designed to statistically compare outcomes between the moderate and high CEACAM5 expression groups. It also lacked control group.

In conclusion, the results of this dose-expansion study demonstrate that when administered as monotherapy, tusamitamab ravtansine 100 mg/m^2 every 2 weeks had a favorable safety profile and produced confirmed ORs in patients with NSq NSCLC. Consistent with earlier parts of the study, reversible corneal events were manageable by dose modifications. Confirmed ORs were observed in approximately 20% of patients with high CEACAM5 expression and in 28% of patients with high CEACAM5 expression and no previous anti-tubulin treatment. Notably, responses to tusamitamab ravtansine were sustained for more than a year in some patients. Thus, CEACAM5-directed ADCs may warrant further exploration as potential treatments for patients with certain CEACAM5-expressing tumors.

CRediT Authorship Contribution Statement

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Disclosure

Dr. Gazzah has received travel, accommodation, and congress registration expenses from Boehringer Ingelheim, Novartis, Pfizer, Roche, and Sanofi; has served in a consultant/expert role for Novartis; has served as principal/subinvestigator of clinical trials for Aduro Biotech, Agios Pharmaceuticals, Amgen, Argenx BVBA, Arno Therapeutics, Astex Pharmaceuticals, AstraZeneca, AVEO, Bayer Healthcare AG, BBB Technologies BV, BeiGene, BioAlliance Pharma, BioNTech AG, Blueprint Medicines, Boehringer Ingelheim, Bristol Myers Squibb, CA, Celgene Corporation, Chugai Pharmaceutical Co., Clovis Oncology, Daiichi Sankyo, Debiopharm S.A., Eisai, Exelixis, Forma, GamaMabs, Genentech, Inc., Gilead Sciences, Inc., GlaxoSmithKline, Glenmark Pharmaceuticals, H3 Biomedicine, Inc., Hoffmann-La Roche AG, Incyte Corporation, Innate Pharma, IRIS Servier, Janssen, Kura Oncology, Kyowa Kirin Pharm, Lilly, Loxo Oncology, Lytix Biopharma AS, MedImmune, Menarini Ricerche, Merck Sharp & Dohme Chibret, Merrimack Pharmaceuticals, Merus, Millennium Pharmaceuticals, Nanobiotix, Nektar Therapeutics, Novartis Pharma, OCTIMET Oncology NV, OncoEthix, OncoMed, Oncopeptides, Onyx Therapeutics, Orion Pharma, Oryzon Genomics, Pfizer, PharmaMar, Pierre Fabre, Rigontec GmbH, Roche, Sanofi Aventis, Sierra Oncology, Taiho Pharmaceutical, Tesaro, Inc., Tioma Therapeutics, Inc., and Xencor; has received research grants from AstraZeneca, Bristol Myers Squibb, Boehringer Ingelheim, Janssen Cilag, Merck, Novartis, Pfizer, Roche, and Sanofi; and reports receiving nonfinancial support (drug supplied) from AstraZeneca, Bayer, Bristol Myers Squibb, Boehringer Ingelheim, Johnson & Johnson, Lilly, MedImmune, Merck, NH TherAguix, Pfizer, and Roche. Dr. Ricordel has received funding from Roche and Novartis and reports that their institution has received funding from AstraZeneca, F. Hoffmann-La Roche, Bristol Myers Squibb, Novartis, and Pfizer. Dr. Italiano reports that their institution has served in a consulting or advisory role for Bayer, Merck Sharp & Dohme, Merck, Roche, Parthenon, Bristol Myers Squibb, PharmaMar, and Novartis; and reports that their institution has received research funding from Bayer, Merck Sharp & Dohme, Merck, Roche, Parthenon, Bristol Myers Squibb, PharmaMar, and Novartis. Dr. Cho is an employee of Yonsei University Health System; reports stock/ownership interests in TheraCanVac Inc., Gencurix Inc., Bridge Biotherapeutics, Kanaph Therapeutics, Cyrus Therapeutics, Interpark Bio Convergence Corp., and J INTS BIO; has served in a consulting or advisory role for Abion, BeiGene, Novartis, AstraZeneca, Boehringer Ingelheim, Roche, Bristol Myers Squibb, CJ Bioscience, Curelogen, Cyrus Therapeutics, ONO, Onegene Biotechnology, Yuhan, Pfizer, Eli Lilly, GI Cell, Guardant Health, HK inno.N, Imnewrun Biosciences Inc., Janssen, Takeda, Merck Sharp & Dohme, MedPacto, Blueprint Medicines, RandBio, and Hanmi; has served as member of the board of directors for Interpark Bio Convergence Corp. and J INTS BIO; has served on advisory boards for Kanaph Therapeutics, Bridge Biotherapeutics, Cyrus Therapeutics, Guardant Health, and Oscotec Inc.; has patents, royalties, and other intellectual property with Champions Oncology, Crown Bioscience, and Imagen; has served as an invited speaker for ASCO, AstraZeneca, Guardant Health, Roche, ESMO, IASLC, Korean Cancer Association, Korean Society of Medical Oncology, Korean Society of Thyroid-Head and Neck Surgery, Korean Cancer Study Group, Novartis, Merck Sharp & Dohme, The Chinese Thoracic Oncology Society, and Pfizer; has other relationships with DAAN Biotherapeutics; and reports their institution has received research funding from MOGAM Institute for Biomedical Research, LG Chem, Oscotec, Interpark Bio Convergence Corp, GI Innovation, GI Cell, Abion, AbbVie, AstraZeneca, Bayer, Blueprint Medicines, Boehringer Ingelheim,

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2025.100844.

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