Safety and efficacy of tusamitamab ravtansine in patients with colorectal or gastric cancer expressing carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5)

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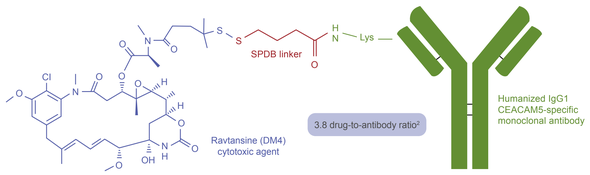
INTRODUCTION

- Carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5) is a glycoprotein that is highly expressed in several types of tumor tissue, including gastrointestinal, lung, and breast, compared with its level of expression in normal epithelial tissue[1]
- Tusamitamab ravtansine is an antibody-drug conjugate composed of a monoclonal antibody that selectively targets CEACAM5-expressing tumor cells linked to a potent, antimitotic cytotoxic maytansinoid, with an antibody:drug ratio of 3.8[2] (**Figure 1**)

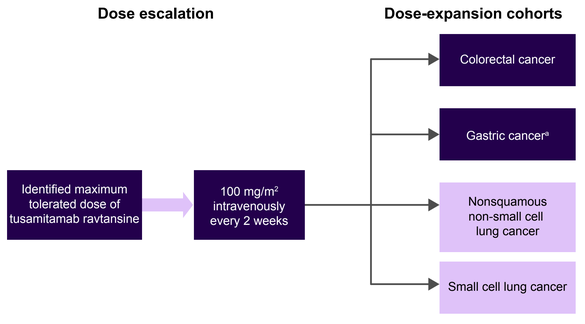
Figure 1. Structure of tusamitamab ravtansine



CEACAM5, carcinoembryonic antigen-related cell adhesion molecule 5; DM4, ravtansine; IgG1, immunoglobulin G1; SPDB, N-succinimidyl 4-(2-pyridyldithio)butyrate.

- The first-in-human Phase 1/2 study of tusamitamab ravtansine (NCT02187848) in patients with advanced solid tumors was conducted in 2 parts (**Figure 2**)

Figure 2. Tusamitamab ravtansine Phase 1/2 study design



[a]Including signet-ring cell carcinoma subtype and gastroesophageal junction adenocarcinomas of the Siewert Types II and III.

- 31 patients were treated in the dose-escalation part of the study, which determined the maximum tolerated dose of tusamitamab ravtansine to be 100 mg/m^2 every 2 weeks (Q2W)[3]
- Patients with different types of cancer were treated at this dose level
  - 92 patients with heavily pretreated nonsquamous non-small cell lung cancer (NSCLC)[4]
    - Among 64 patients with NSCLC that highly expressed CEACAM5 (≥ 2+ intensity in ≥ 50% of tumor cells), there were 13 patients with confirmed partial response (PR) and 28 patients with stable disease (SD) for an objective response rate (ORR) of 20.3%
    - Among 28 patients with NSCLC that moderately expressed CEACAM5 (≥ 2+ intensity in ≥ 1% of tumor cells but < 50%), there were 2 patients with confirmed PR and 15 patients with SD for an ORR of 7.1%
  - In addition, 25 patients with colorectal cancer (CRC; n = 18) or gastric cancer (GC; n = 7) were treated at various dose levels. There were 2 confirmed PRs among the patients with CRC and 1 confirmed PR among the patients with GC[3]
- Here, we report the efficacy and safety of tusamitamab ravtansine in patients with CRC and GC in the expansion part of the study

METHODS

Patients

- Eligible patients were at least 18 years of age; had locally advanced or metastatic CRC, irrespective of CEACAM5 expression, or GC (including signet-ring cell carcinoma subtype and gastroesophageal junction adenocarcinomas of Siewert Types II and III) with prospectively demonstrated CEACAM5 expression in the most recent formalin-fixed paraffin-embedded archival tumor tissue sample at ≥ 2+ in intensity in ≥ 50% of the tumor cell population; had measurable disease; had at least one lesion that could be biopsied; and had Eastern Cooperative Oncology Group performance status 0 or 1
- Exclusion criteria included prior treatment with maytansinoids or treatments targeting CEACAM5, concurrent anticancer therapy, known or symptomatic brain metastasis or leptomeningeal carcinomatosis, laboratory results indicating poor organ function or bone marrow reserve, significant concomitant illnesses including any condition requiring concomitant treatment with a strong cytochrome P-450 CYP3A inhibitor, prior history of or unresolved corneal disorders, and unresolved (Grade > 1) signs and symptoms of neuropathy

Study Design

- This was an open-label, nonrandomized study (**Figure 2**)
- Eligible patients were treated with intravenous tusamitamab ravtansine 100 mg/m^2 Q2W

Endpoints

- The primary efficacy endpoint was overall objective response (confirmed complete response [CR] or PR) using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 in all patients who received tusamitamab ravtansine
- Secondary endpoints included duration of response for patients with a confirmed response and time to progression (TTP) for the all-treated population
- Treatment-emergent adverse events (TEAEs) were characterized according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 and coded using the Medical Dictionary for Regulatory Activities version 23.1

RESULTS

- A total of 46 patients with CRC and 16 patients with GC were treated with tusamitamab ravtansine 100 mg/m^2 Q2W in the dose-expansion part of the study
- In both cohorts, all patients had measurable disease, and at least half of patients in both cohorts had CEACAM5 expression (≥ 2+ intensity) in at least 80% of tumor cells (**Table 1**)

Table 1. Baseline demographic and disease characteristics

Characteristic	CRC (n = 46)	GC (n = 16)
Age, years, median (range)	62 (36–77)	59 (35–77)
Female, n (%)	13 (28)	3 (19)
ECOG PS, n (%)		
0	19 (41)	3 (19)
1	27 (59)	13 (81)
Number of prior regimens, n, median (range)	4 (1–9)	3 (1–6)
Prior antitubulin status, n (%)	0	13 (81)
Proportion of tumor cells with CEACAM5 expression ≥ 2+ intensity, n/N (%)[a]		
< 50%	7/44 (16)	0
50%–80%	11/44 (25)	8/16 (50)
≥ 80%	26/44 (59)	8/16 (50)
Circulating CEA level, µg/L, median (range)	121.85 (1.8–41,227)	148.20 (1.2–4028.0)

CEA, carcinoembryonic antigen; CEACAM5, carcinoembryonic antigen-related cell adhesion molecule 5; CRC, colorectal cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; GC gastric cancer.
[a]Among patients who had archival tumor samples.

- In the CRC cohort,
  - The median duration of treatment was 8.0 weeks (range: 2.0–23.1 weeks)
  - The median number of cycles per patient was 4.0 (range: 1.0–11.0 cycles)
  - The mean (standard deviation) relative dose intensity (actual dose intensity / planned dose intensity) was 0.96 (0.11), and the median actual dose intensity (cumulative dose / actual number of weeks on treatment) was 49.50 mg/m^2/week (range: 29.9–56.8 mg/m^2/week)
- In the GC cohort,
  - The median duration of treatment was 8.0 weeks (range: 2.0–22.0 weeks)
  - The median number of cycles per patient was 4.0 (range: 1.0–11.0 cycles)
  - The mean (standard deviation) relative dose intensity was 0.97 (0.05), and the median actual dose intensity was 49.41 mg/m^2/week (range: 41.3–50.6 mg/m^2/week)

Efficacy

- Although some treatment response was observed during the dose-escalation phase, none of the 46 patients with CRC or 16 patients with GC had a confirmed CR or PR
- The best overall response was SD in 12 patients with CRC and 6 patients with GC (**Table 2**)
- Median TTP in the CRC and GC cohorts was 1.8 months (95% confidence interval [CI]: 1.64–1.91) and 1.7 months (95% CI: 1.18–2.60), respectively

Table 2. Best overall response in CRC and GC dose-expansion cohorts

Best overall response, n (%)	CRC (n = 46)	GC (n = 16)
CR[a]	0	0
PR[a]	0[b]	0
SD	12 (26)	6 (38)
PD	26 (57)	9 (56)
Not evaluable[c]	8 (17)	1 (6)

CI, confidence interval; CR, complete response; CRC, colorectal cancer; GC, gastric cancer; PD, progressive disease; PR, partial response; SD, stable disease.
[a]Confirmation of response was required to be documented as a confirmed response. [b]One patient had an unconfirmed response. [c]Includes patients with no post-baseline evaluation due to early death or early progression based on symptomatic deterioration.

Safety

- TEAEs (**Table 3**) occurred in 97.8% of patients with CRC and 87.5% of patients with GC
- Treatment-related adverse events (TRAEs) occurred in 34 (73.9%) patients with CRC and 9 (56.3%) patients with GC
- The most frequent TRAEs in the CRC cohort were asthenia (26.1%), keratitis (15.2%), nausea (15.2%), diarrhea (10.9%), and keratopathy (10.9%)
  - Grade ≥ 3 TRAEs occurred in 7 patients (15.2%), including keratopathy in 2 patients (4.3%)
- The mean (standard deviation) time to recovery from corneal TEAEs was 24.2 (11.5) days among patients with CRC and 15.0 (4.2) days among those with GC

Table 3. TEAEs occurring in ≥ 10% of patients with CRC and GC

	CRC (N = 46)		GC (N = 16)	
Adverse event, n (%)	**Any grade**	**Grade ≥ 3**	**Any grade**	**Grade ≥ 3**
Any event	45 (97.8)	23 (50.0)	14 (87.5)	9 (56.3)
Asthenia	15 (32.6)	2 (4.3)	6 (37.5)	1 (6.3)
Keratitis/keratopathy	14 (30.4)	2 (4.3)	2 (12.5)	0
Keratitis	8 (17.4)	0	1 (6.3)	0
Keratopathy	6 (13.0)	2 (4.3)	1 (6.3)	0
Nausea	11 (23.9)	0	3 (18.8)	0
Constipation	10 (21.7)	0	2 (12.5)	0
Decreased appetite	10 (21.7)	2 (4.3)	5 (31.3)	1 (6.3)
Diarrhea	10 (21.7)	0	1 (6.3)	0
Abdominal pain	7 (15.2)	0	3 (18.8)	0
Dyspnea	5 (10.9)	1 (2.2)	3 (18.8)	0
Fatigue	5 (10.9)	1 (2.2)	4 (25.0)	0
Pyrexia	5 (10.9)	0	1 (6.3)	0
Vomiting	5 (10.9)	0	2 (12.5)	1 (6.3)
Back pain	4 (8.7)	0	3 (18.8)	0
Disease progression	4 (8.7)	4 (8.7)	3 (18.8)	3 (18.8)
Anemia	0	0	2 (12.5)	1 (6.3)
Ascites	0	0	2 (12.5)	1 (6.3)
Dizziness	0	0	2 (12.5)	0
Dry eye	0	0	2 (12.5)	0
Dyspepsia	0	0	3 (18.8)	0
Peripheral edema	0	0	2 (12.5)	0

- The most frequent TRAEs in the GC cohort were asthenia (25%), decreased appetite (18.8%), fatigue (18.8%), back pain (12.5%), dry eye (12.5%), and nausea (12.5%)
  - Grade ≥ 3 TRAEs occurred in 2 patients (12.5%), neither of which were ocular related
- Corneal TRAEs (keratitis and keratopathy) occurred in 13 (28.3%) and 2 (12.5%) patients in the CRC and GC cohorts, which led to treatment modification in 5 (10.9%) patients and 1 (6.3%) patient, respectively
  - No patients required treatment discontinuation due to corneal events

CONCLUSIONS AND FUTURE DIRECTIONS

- **Tusamitamab ravtansine 100 mg/m^2 Q2W was well tolerated in patients with CRC and GC**
- **In patients with GC who were pretreated with taxanes, tusamitamab ravtansine 100 mg/m^2 Q2W showed modest disease control**
- **Further development of tusamitamab ravtansine should focus on combination therapy in CRC and patients with GC who are taxane-naïve**

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