1261TIP

CARMEN-GC01: Phase 2, open-label, single-arm study of tusamitamab ravtansine in combination with ramucirumab in pretreated patients with gastric or gastroesophageal junction adenocarcinoma (GA/GEJA)

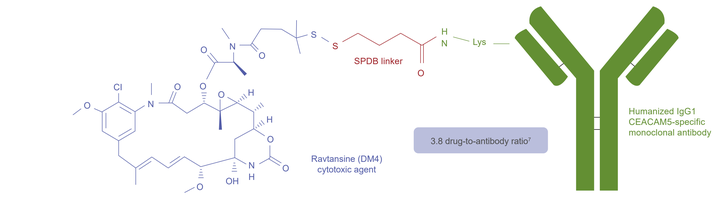
Francis Maria Esposito[1], Jeeyun Lee[2], Sun Young Rha[3], Konstantin Penkov[4], Alexey Moisseev[5], Marc Van den Eynde[6], Hans Prenen[7], Marc Díez García[8], Mahmut Gumus[9], Tamotsu Sagawa[10], Marina Nechaeva[11], Takeshi Kajiwara[12], Hakan Harputluoglu[13], Laure Charbonnier[14],Samira Bensfia[15], Nan Yang[16], Do-Youn Oh[17]

[1]Medical Oncology Department/ICMHO, Hospital Clínic de Barcelona, Barcelona, Spain; [2]Department of Hematology-Oncology, Samsung Medical Center, Seoul, Republic of Korea; [3]Department of Medical Oncology, Yonsei Cancer Center, Yonsei University Health System, Seoul, Republic of Korea; [4]Oncology Department, Euromedservice, St. Petersburg, Russia; [5]Medical Oncology and Gastroenterology Department, Medical Clinic of NACPP, Moscow, Russia; [6]Oncology and Gastroenterology Department, Cliniques Universitaires Saint-Luc, Brussels, Belgium; [7]Oncology Department, UZA, Edegem, Belgium; [8]Medical Oncology Department, Hospital Universitario Vall d'Hebron, Barcelona, Spain; [9]Medical Oncology Department, Istanbul Medeniyet University, Istanbul, Turkey; [10]Gastroenterology Department, National Hospital Organization Hokkaido Cancer Center, Sapporo, Hokkaido, Japan; [11]Clinical Oncological Dispensary, State Budgetary Healthcare Institution of Arkhangelsk Region, Arkhangelsk, Russia; [12]Department of Gastrointestinal Medical Oncology, National Hospital Organization Shikoku Cancer Center, Matsuyama, Ehime, Japan; [13]Medical Oncology Department, Inonu University Turgut Ozal Medical Center, Malatya, Turkey; [14]Biostatistics & Programming, Sanofi, Chilly-Mazarin, France; [15]Clinical Development, Sanofi, Cambridge, MA, USA; [16]Clinical Development, Sanofi, Shanghai, China; [17]Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea

BACKGROUND

- For patients with gastric cancer (GC), including gastric adenocarcinoma (GA) or gastric esophageal junction adenocarcinoma (GEJA), ramucirumab, an antibody antagonist of vascular endothelial growth factor receptor 2 (VEGFR2), combined with paclitaxel is a standard-of-care option for second-line (2L) treatment; however, real-world overall survival is less than 1 year, indicating the need for additional treatment options[1, 2]
- Carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5), a member of the carcinoembryonic antigen family, is weakly expressed on the surface of normal epithelial tissues but has elevated expression levels in some cancer types, including GA[3, 4]
- High CEACAM5 expression occurs in 30% of patients with GC[5]
- Tusamitamab ravtansine (SAR408701) is an antibody-drug conjugate that combines a humanized CEACAM5-targeting monoclonal antibody with the potent antitubulin agent ravtansine (DM4) via a glutathione-cleavable linker[4, 6] (**Figure 1**)

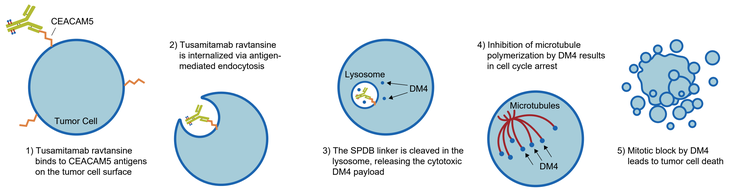
Figure 1. Tusamitamab ravtansine: an anti-CEACAM5 ADC with a cleavable linker[7]



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

- Tusamitamab ravtansine binds selectively to the extracellular domain of CEACAM5 on tumor cells, resulting in delivery of ravtansine into the tumor cell, followed by cell cycle arrest and apoptosis due to the inhibition of microtubule assembly (**Figure 2**)[4, 8]

Figure 2. Mechanism of action of tusamitamab ravtansine[4, 8]



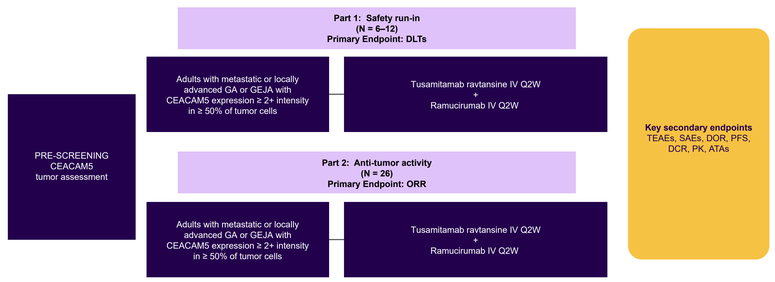
CEACAM5, carcinoembryonic antigen-related cell adhesion molecule 5; DM4, ravtansine; SPDB, N-succinimidyl 4-(2-pyridyldithio)butyrate.

- Tusamitamab ravtansine 100 mg/m^2 every 2 weeks (Q2W) demonstrated promising antitumor activity in the first-in-human, Phase 1/2 study (NCT02187848) in a cohort of heavily pretreated patients with advanced nonsquamous non-small cell lung cancer (NSCLC) and high CEACAM5 expression (defined as ≥ 2+ CEACAM5 intensity in ≥ 50% of the tumor cells as determined by immunohistochemistry [IHC])[9, 10]
  - Some patients in this cohort have remained on treatment for ≥ 12 months[11]
- Preclinical studies with tusamitamab ravtansine and a VEGFR2 antagonist have shown synergistic activity in patient-derived gastric xenografts, supporting clinical investigation of tusamitamab ravtansine in combination with ramucirumab[5]
  - The combination of tusamitamab ravtansine plus ramucirumab may lead to improved 2L outcomes in patients with GA or GEJA, with a better safety profile compared with that of paclitaxel plus ramucirumab
- A Phase 2 study (NCT04394624) of tusamitamab ravtansine in combination with ramucirumab is ongoing in patients with NSCLC with high CEACAM5 expression
- Results from the Phase 1/2 study for a cohort of patients with gastric cancer who received tusamitamab ravtansine as monotherapy are presented in a poster at ESMO 2022 (Italiano A, et al., Poster 490P)
- Here, we report the study design of CARMEN-GC01 (NCT05071053; EudraCT: 2021-001976-26), which is evaluating tusamitamab ravtansine in combination with ramucirumab in patients with GA or GEJA with high CEACAM5-expressing tumors

STUDY OVERVIEW

- CARMEN-GC01 is a Phase 2, open-label, single-arm, multicenter, 2-part study to evaluate tusamitamab ravtansine combined with ramucirumab Q2W in previously treated patients with GA or GEJA with high CEACAM5 expression (**Figure 3**)
  - Part 1 is a safety run-in, which will be followed by a Part 2 expansion
- The primary objectives are to confirm the recommended tusamitamab ravtansine loading dose in combination with ramucirumab (Part 1) and to assess the antitumor activity of tusamitamab ravtansine in combination with ramucirumab in advanced GA or GEJA (Part 2)
- Key secondary objectives are to assess safety and tolerability, duration of response, progression-free survival, disease control rate, pharmacokinetics, and immunogenicity

Figure 3. Trial design for CARMEN-GC01



ATA, anti-therapeutic antibody; CEACAM5, carcinoembryonic antigen-related cell adhesion molecule 5; DCR, disease control rate; DLT, dose-limiting toxicity; DOR, duration of response; GA, gastric adenocarcinoma; GEJA, gastroesophageal junction adenocarcinoma; IV, intravenous; ORR, objective response rate; PFS, progression-free survival; PK, pharmacokinetics; Q2W, every 2 weeks; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

STUDY ENDPOINTS

Primary Endpoints

- Part 1: Incidence of study-drug-related dose-limiting toxicities
- Part 2: Objective response rate, defined as the proportion of participants who have confirmed complete response (CR) or partial response (PR) as best overall response per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1

Secondary Endpoints

- Incidence of treatment-emergent adverse events, serious adverse events, and laboratory abnormalities according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0
- Duration of response (time from first documented evidence of CR or PR until progressive disease per RECIST version 1.1 or death from any cause)
- Progression-free survival (time from the date of first administration to the date of first documented disease progression or death due to any cause)
- Disease control rate, defined as the percentage of patients with confirmed CR, PR, or stable disease as best overall response per RECIST version 1.1
- Incidence of anti-therapeutic antibodies against tusamitamab ravtansine
- Pharmacokinetic parameters of tusamitamab ravtansine and ramucirumab

PATIENT ELIGIBILITY

Key Inclusion Criteria

- Patients ≥ 18 years old
- Histologically or cytologically confirmed diagnosis of GA or GEJA
- Metastatic disease or locally advanced, unresectable disease
- At least one measurable lesion by RECIST version 1.1
- CEACAM5 expression of ≥ 2+ intensity in archival tumor sample or fresh biopsy sample involving ≥ 50% of the tumor cell population as demonstrated prospectively by central laboratory via IHC
- Documented disease progression during or after first-line therapy containing platinum and/or fluoropyrimidine agents, and if appropriate, human epidermal growth factor receptor 2 therapy. No more than 1 prior chemotherapy line
- Eastern Cooperative Oncology Group performance status of 0 or 1

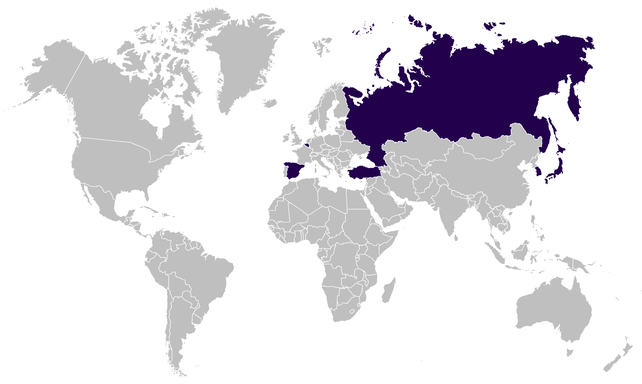
Key Exclusion Criteria

- Untreated brain metastases, leptomeningeal disease, or uncontrolled spinal cord compression
- Significant concomitant illness
- History within the last 3 years of an invasive malignancy other than GA or GEJA
- History of gross hemoptysis in prior 2 months
- Gastrointestinal perforation and/or fistula within the prior 6 months or Grade 3-4 gastrointestinal bleeding within the prior 3 months
- Bowel obstruction; history or presence of inflammatory enteropathy; or extensive intestinal resection, Crohn's disease, ulcerative colitis, or chronic diarrhea
- Major surgery in the prior 28 days
- Unresolved Grade ≥ 2 toxicity according to NCI CTCAE version 5.0 related to prior treatment, except for alopecia, vitiligo, and active thyroiditis controlled with hormone replacement therapy
- Unresolved corneal disorder or any previous corneal disorder considered by an ophthalmologist to predict higher risk of drug-induced keratopathy
- Use of contact lenses is not permitted
- Concurrent treatment with any other anticancer therapy
- Prior treatment with ramucirumab or a taxane
- Prior treatment targeting CEACAM5, vascular endothelial growth factor, or vascular endothelial growth factor receptor
- Prior treatment containing a maytansinoid (DM1 or DM4)
- Poor organ function

STUDY SITES

- As of July 8, 2022, there are 23 active sites in 6 countries, of which 21 sites are recruiting. (**Figure 4**)

Figure 4. Countries with active sites



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DISCLOSURES:

- **SYR** has served in a consulting or advisory role for Amgen, GSK, Indivumed, LG Biochemical, and MSD; reports their institution has received research funding/grants from BMS, Daiichi Sankyo, Lilly, and MSD; has served in a speakers bureau for Amgen, BeiGene, Indivumed, Lilly, MSD, and Zymeworks; and has received drug supply for a clinical trial from Merck and MSD.
- **KP** has served in a consulting or advisory role for Nektar and reports their institution has received research funding/grants from AstraZeneca, Janssen, Merck Sharp & Dohme, Nektar, Novartis, Pfizer, Regeneron Pharmaceuticals, Roche, Takeda, and Yuhan.
- **MVDE** has served in a consulting or advisory role for Amgen, BMS, Merck, MSD, Pierre Fabre, and Servier and reports their institution has received research funding/grants from Merck.
- **HP** has served in a consulting or advisory role for Amgen, AstraZeneca, and Roche and has served in a speakers bureau for Bayer, Ipsen, and Sanofi.
- **MG** has served in a consulting or advisory role for MSD, Novartis, and Roche; reports their institution has received research funding/grants from Amgen and Roche; and reports honoraria from Astellas, Janssen, Novartis, Pfizer, and Roche.
- **TK** reports honoraria from Chugai Pharmaceutical Co., Ltd., Eli Lilly Japan K.K., Ono Pharmaceutical Co., Ltd., and Taiho Pharmaceutical Co., Ltd.
- **LC, SB,** and **NY** are employees of Sanofi and report stock/ownership interests in Sanofi.
- **D-YO** has served in a consulting or advisory role for Arcus Biosciences, ASLAN, AstraZeneca, Basilea, Bayer, BeiGene, BMS/Celgene, Genentech/Roche, Halozyme, IQVIA, Merck Serono , Novartis, Taiho, Turning Point, Yuhan, and Zymeworks and reports their institution has received research funding/grants from Array, AstraZeneca, BeiGene, Eli Lilly, Handok, MSD, Novartis, and Servier.
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