CARMEN-LC04: Phase 2 single-arm trial of safety, antitumor activity, and pharmacokinetics of tusamitamab ravtansine (SAR408701) plus ramucirumab in carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5)-positive, metastatic, non-squamous, non-small cell lung cancer progressing on platinum-based chemotherapy and immunotherapy

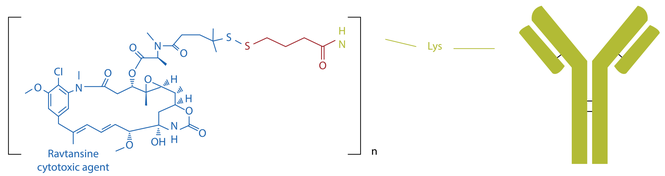
Byoung Chul Cho[1], Carlos Aguado de la Rosa[2], Laia Vilà[3], Dolores Isla[4], Julio Oliveira[5], Javier de Castro Carpeño[6], Antoaneta Tomova[7], Tae Min Kim[8], Ana Blasco Cordellat[9], Anne-Laure Bauchet[10], Christine Soufflet[11], Samira Bensfia[12], Grace K. Dy[13]

[1]Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea; [2]Hospital Clinico San Carlos, Madrid, Spain; [3]Parc Taulí Hospital Universitari, Sabadell, Barcelona, Spain; [4]Hospital Clínico Universitario Lozano Blesa, Zaragoza, Spain; [5]Instituto Português de Oncologia do Porto Francisco Gentil E.P.E., Porto, Portugal; [6]Hospital Universitario La Paz, Madrid, Spain; [7]Complex Oncology Center Plovdiv, Plovdiv, Bulgaria; [8]Seoul National University Hospital, Seoul, Republic of Korea; [9]Hospital Universitario de Valencia, Valencia, Spain; [10]Sanofi, Chilly-Mazarin, France; [11]Excelya on behalf of Sanofi, Boulogne-Billancourt, France; [12]Sanofi, Cambridge, MA, USA; [13]Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA

BACKGROUND

- Lung cancer is the leading cause of cancer death worldwide[1]
  - In the US, non-small cell lung cancer (NSCLC) accounts for 89% of new lung cancer cases, and 78% of NSCLC cases have non-squamous (NSQ) histology[2]
- In patients with metastatic NSCLC lacking targetable genomic aberrations who progress on immunotherapy and platinum-based chemotherapy, treatment options are generally limited to docetaxel ± a vascular endothelial growth factor inhibitor such as ramucirumab[3]
  - Toxicity associated with current treatment combinations necessitates the development of new therapeutics
- CEACAM5 is overexpressed on the surface of multiple epithelial tumors, including NSCLC, compared with normal tissues and is involved in cell adhesion, invasion, and metastasis[4]
  - In a large panel of normal and malignant tissue samples, CEACAM5 membrane expression (of any positivity level) occurred in 38% of cases in NSCLC adenocarcinoma versus 0% in normal lung tissue[4]
- Tusamitamab ravtansine (SAR408701) is an antibody-drug conjugate (ADC) that combines a humanized CEACAM5-targeting antibody with the potent maytansinoid derivative ravtansine (DM4) via a cleavable linker with a drug-to-antibody ratio of 3.8 (**Figure 1**)[4,5]
  - Ravtansine is a microtubule assembly inhibitor with potent cytotoxic antitumor activity

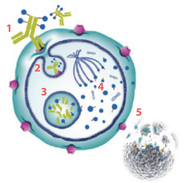
Figure 1. Tusamitamab ravtansine: an anti-CEACAM5 ADC with a cleavable linker



n indicates a drug-to-antibody ratio of 3.8[5]
ADC, antibody-drug conjugate; CEACAM5, carcinogenic antigen-related cell adhesion molecule 5.

- Selective binding of the antibody portion of tusamitamab ravtansine to the extracellular domain of CEACAM5 results in internalization of tusamitamab ravtansine and selective delivery of ravtansine into the tumor cell, where it inhibits microtubule assembly resulting in cell cycle arrest and apoptosis (**Figure 2**)[4,6]
  - Selective delivery of the cytotoxic agent may reduce systemic toxicity

Figure 2. Mechanism of action of tusamitamab ravtansine



1. Antibody portion of tusamitamab ravtansine binds to extracellular domain of CEACAM5
2. Internalization of tusamitamab ravtansine
3. Release of DM4 into the tumor cell
4. Inhibition of microtubule assembly
5. Cell cycle arrest and apoptosis

CEACAM5, carcinogenic antigen-related cell adhesion molecule 5; DM4, maytansinoid derivative cytotoxic agent.
 DOI: 10.1358/dof.2016.041.09.2544475.

- Tusamitamab ravtansine has demonstrated preclinical antitumor activity in CEACAM5-expressing tumor cell lines and patient-derived xenograft models[4]
- Tusamitamab ravtansine has demonstrated promising antitumor activity in heavily pretreated patients with advanced NSQ NSCLC and high CEACAM5 expression (n = 64) and was well tolerated (NCT02187848)[7]
  - The objective response rate (ORR) was 20.3%
  - Hematological toxicity was minimal compared with conventional chemotherapy
  - The most frequent treatment-emergent adverse events (all grades) in patients with moderate or high CEACAM5 expression (n = 92) were asthenia (38.0%), keratopathy/keratitis (38.0%), peripheral neuropathy (26.1%), dyspnea (23.9%), and diarrhea (22.8%)
- Here, we report the design of CARMEN-LC04 (NCT04394624), which evaluates the safety and antitumor activity of tusamitamab ravtansine combined with ramucirumab in high CEACAM5-expressing NSQ NSCLC tumors

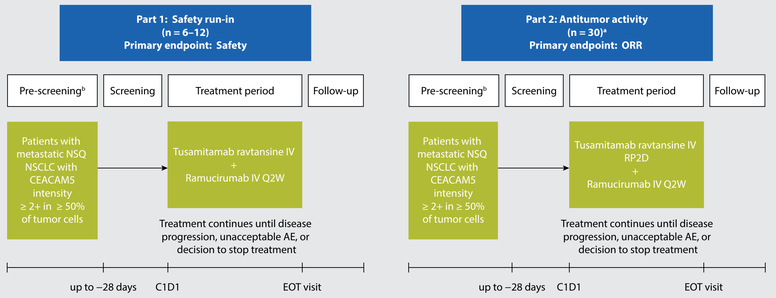
STUDY OVERVIEW

- CARMEN-LC04 is a Phase 2, open-label, single arm, multicenter, international study assessing the safety, antitumor activity, and pharmacokinetics of the combination of tusamitamab ravtansine and ramucirumab in patients with metastatic NSQ NSCLC with high CEACAM5-expressing tumors, who were previously treated with platinum-based chemotherapy and an immune checkpoint inhibitor
  - High CEACAM5 expression was defined as CEACAM5 intensity ≥ 2+ in ≥ 50% of tumor cells by immunohistochemistry
- Enrollment is planned to achieve up to 36 treated patients total

Study Design

- Part 1 (Safety run-in, **Figure 3**)
  - Part 1 will determine the recommended Phase 2 dose (RP2D) of tusamitamab ravtansine in combination with ramucirumab based on dose-limiting toxicity (DLT)
  - Treatments: antihistamines preceding an intravenous (IV) infusion of ramucirumab, followed by an IV infusion of tusamitamab ravtansine, every 2 weeks
- Part 2 (Antitumor activity, **Figure 3**)
  - Treatments: antihistamines preceding an IV infusion of ramucirumab, followed by an IV infusion of tusamitamab ravtansine at the RP2D determined in Part 1, every 2 weeks

Figure 3. CARMEN-LC04 study design schema



[a]n = 30 to include the 6 patients in Part 1 who received the RP2D.
[b]Patient's tumor tissue (archival or, if not available, new fresh biopsy) will be analyzed for CEACAM5-positive status; only patients whose tumor had CEACAM5 expression level of ≥ 2+ intensity in ≥ 50% of the tumor cell population will be screened.
AE, adverse event; C1D1, Cycle 1/Day 1; CEACAM5, carcinoembryonic antigen-related cell adhesion molecule 5; EOT, end of treatment; IV, intravenous; NSCLC, non-small cell lung cancer; NSQ, non-squamous; ORR, objective response rate; Q2W, every 2 weeks; RP2D, recommended Phase 2 dose.

STUDY ENDPOINTS

- Primary endpoints
  - Part 1:
    - DLT at Cycle 1 and Cycle 2
    - Determination of the RP2D of tusamitamab ravtansine in combination with ramucirumab
  - Part 2: ORR
- Secondary endpoints (Parts 1 and 2)
  - Safety and tolerability
  - Duration of response
  - Progression-free survival
  - Pharmacokinetics of tusamitamab ravtansine and ramucirumab
  - Incidence of anti-therapeutic antibodies against tusamitamab ravtansine

PATIENT CRITERIA

Key Inclusion Criteria

- ≥ 18 years of age
- Proven high CEACAM5-expressing metastatic NSQ NSCLC, defined as CEACAM5 intensity ≥ 2+ in ≥ 50% of tumor cells by immunohistochemistry
- Metastatic disease progression fulfilling both of the following 2 criteria:
  - Disease progression during or after platinum-based chemotherapy (at least 2 cycles). Maintenance therapy following platinum-based chemotherapy is not considered as a separate regimen. Adjuvant/neoadjuvant treatment for a patient who had a relapse with metastatic disease during or within 6 months of completing treatment will be considered as first-line treatment
  - Disease progression during or after 1 immune checkpoint inhibitor (anti-programmed cell death protein 1/programmed cell death ligand 1). This could be given as monotherapy or in combination with platinum-based chemotherapy (whatever the order)
- In patients with *EGFR* or *BRAF* mutations or *ALK/ROS* alterations, disease progression while receiving the corresponding approved, targeted-therapy in addition to platinum-based chemotherapy and an immune checkpoint inhibitor
- ≥ 1 measurable lesion by Response Evaluation Criteria in Solid Tumors v1.1 as determined by local site investigator assessment
- Eastern Cooperative Oncology Group performance status 0–1

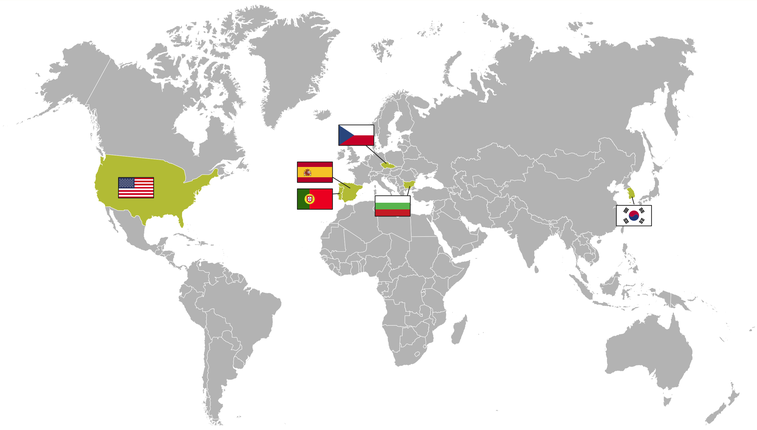
Key Exclusion Criteria

- Untreated brain metastases and history of leptomeningeal disease
- Unresolved corneal disorder or any previous corneal disorder that increases risk of drug-induced keratopathy
- Concurrent treatment with any other anticancer therapy
- > 1 previous chemotherapy in metastatic setting
- Prior treatment with ramucirumab or docetaxel
- Prior therapy targeting CEACAM5 or prior maytansinoid treatment

STUDY SITES

- This study is being conducted at 18 study sites in 6 countries (**Figure 4**) and is actively recruiting participants
  - Part 1 recruitment is complete
  - Part 2 recruitment is ongoing

Figure 4. Global enrollment



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Presented at the ESMO 2021 Virtual Scientific Program. September 16–21, 2021.

DISCLOSURES

BCC has stock from TheraCanVac Inc, Gencurix Inc, Bridge Biotherapeutics, KANAPH Therapeutics Inc, Cyrus Therapeutics, and Interpark Bio-Convergence Corp; has served as a consultant for Novartis, AstraZeneca, Boehringer-Ingelheim, Roche, BMS, Ono, Yuhan, Pfizer, Eli Lilly, Janssen, Takeda, MSD, MedPacto, and Blueprint Medicines; has served on an advisory board for KANAPH Therapeutic Inc, Bridge Biotherapeutics, Cyrus Therapeutics, and Guardant Health; has received research grants from Novartis, Bayer, AstraZeneca, the MOGAM Institute, Dong-A ST, Champions Oncology, Janssen, Yuhan, Ono, Dizal Pharma, MSD, AbbVie, MedPacto, GI Innovation, Eli Lilly, Blueprint Medicines, and Interpark Bio Convergence Corp; serves on the board of directors for Interpark Bio Convergence Corp; receives royalties from Champions Oncology; and is the founder of DAAN Biotherapeutics. CAR has served as a consultant or on an advisory board for Roche, Sanofi, Pierre Fabre, Novartis, BMS, AstraZeneca, and Boehringer; and has received honoraria from Roche, Sanofi, MSD, BMS, and AstraZeneca. LV has served as a consultant or on an advisory board for Roche Pharma SA, Boehringer Ingelheim, and AstraZeneca; has received a research grant from AstraZeneca; and has received honoraria from Bristol Myers Squibb, Merck, and Roche Pharma. JO has served as a consultant or on an advisory board for Bayer, AstraZeneca, Roche, and Eisai; and has received a research grant from AstraZeneca. JCC has served as a consultant or on an advisory board for AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Janssen, Lilly, Merck Sharp & Dohme, Novartis, Pfizer, Roche, and Takeda; and has participated in the speakers bureau for AstraZeneca, Bristol Myers Squibb, Merck Sharp & Dohme, and Roche. TMK has served as a consultant or on an advisory board for AstraZeneca, Boryung, Hanmi, Novartis, Takeda, Sanofi, and Roche/Genentech; has received a research grant from AZ-KHIDI (outside of this work); and has received honoraria from AstraZeneca, Hanmi, and Takeda. CS is an employee of Excelya on behalf of Sanofi. A-LB and SB are employees of Sanofi and may hold shares and/or stock options in the company. DI, AT, ABC, and GKD have no disclosures to report.

ACKNOWLEDGMENTS

- Research and analyses were supported by Sanofi
- The authors were responsible for all content and editorial decisions
- Editorial support was provided by Elizabeth Strickland, PhD, and Julian Martins, MA, inScience Communications (Philadelphia, PA, USA), funded by Sanofi

For any medical questions please contact Byoung Chul Cho, CBC1971@yuhs.ac