Sponsor: Sanofi **Drug substance(s):** SAR408701 - tusamitamab ravtansine	**Study Identifiers:** EudraCT/EU trial number: 2021-001967-26 NCT: NCT05071053 **Study code:** ACT16444

Title of the study:

Open-label study of tusamitamab ravtansine (SAR408701) in combination with ramucirumab in participants previously treated for advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma with CEACAM5-positive tumors

Study center(s):

This study was conducted at 23 centers that enrolled participants in Japan, Korea, Russia, Belgium, Spain, and Turkey.

Study period:

Date first study participant enrolled: 29 November 2021

Date last study participant completed: 05 November 2024.

Study Status: Terminated, due to discontinuation of overall development of tusamitamab ravtansine (SAR408701) by the Sponsor on 20 Dec 2023.

Phase of development: Phase 2

Objectives:

Primary

The primary objective of Part 1 of the study was to confirm the tusamitamab ravtansine dosage regimen in combination with ramucirumab based on incidence of dose-limiting toxicities in the first 2 cycles.

The primary objective of Part 2 of the study was to assess the antitumor activity of this combination regimen, as assessed by objective response rate (proportion of participants with confirmed complete response or partial response as best overall response).

Secondary

Secondary objectives were to assess the safety and tolerability of this combination as assessed by treatment emergent adverse events and clinical laboratory abnormalities; to evaluate progression- free survival; to evaluate disease control rate (proportion of participants with confirmed complete or partial responses or stable disease as best overall response); to evaluate the pharmacokinetic (PK) of tusamitamab ravtansine when in administered in combination with ramucirumab, and to assess the immunogenicity of tusamitamab ravtansine when administered in combination with ramucirumab.

Methodology:

This is a single group, treatment, Phase 2, open-label, single-arm study to confirm the recommended dose (RD), safety, PK, and preliminary antitumor activity of tusamitamab ravtansine combined with ramucirumab in participants previously treated for gastric or gastroesophageal adenocarcinoma with CEACAM5-positive (defined as CEACAM5 immunohistochemical (IHC) intensity ≥2+ in ≥50% of cells) tumors.

This was a 2-part study.

Part 1 (safety run-in): Participants received ramucirumab 8 mg/kg followed by tusamitamab ravtansine at 170 mg/m2 at Day 1 Cycle 1, and ramucirumab 8 mg/kg followed by tusamitamab ravtansine 100 mg/m2 at Cycle 2 and every 2 weeks (Q2W) in all subsequent cycles. Enough participants were enrolled in Part 1 to achieve 6 to 12 participants evaluable for dose-limiting toxicities (DLTs) to confirm the recommended dose. The DLT observation period was the first 2 cycles (approximately 28 days). A minimum delay of 1 week was required between the initial dose in the first participant treated in a dose level (DL) cohort and dosing of the next 2 participants treated at the same DL.

Part 2 of the study: The recommended dose confirmed in Part 1 was evaluated for activity in 26 additional participants. A total of 35 participants, including participants treated at the recommended dose in Part 1, were evaluated for activity.

Number of study participants:

A total of 38 participants were planned for the study. A total of 45 participants were screened and 35 participants were enrolled in the study. All of them (N=35) had completed the study intervention at the time of the CSR addendum cut-off (05 November 2024). The 2 participants, still under study intervention at the cut-off date of abbreviated CSR, permanently discontinued the intervention due to disease progression. Consequently, 30 participants (85.7%) discontinued the study intervention due to disease progression and 5 participants (14.3%) discontinued due to AEs. None of the participants permanently discontinued the full intervention or withdrew the participation due to a reason related to COVID-19 (Table1).

Table 1 - Participant disposition - All-treated population

	Tusa rav 170 mg/m² at C1D1, then 100 mg/m² + ramucirumab (N=35)
Enrolled and not exposed	0
Enrolled and exposed[n(%)]	35 (100)
Still on treatment	0
Permanent full study intervention discontinuation	35 (100)
Reason for permanent full study intervention discontinuation	
Adverse event	5 (14.3)
Related to COVID-19	0
Not related to COVID-19	5 (14.3)
Progressive disease	30 (85.7)
Poor compliance to protocol	0
Withdrawal by subject	0
Othera	0
Related to COVID-19	0
Not related to COVID-19	0
Reason for study intervention withdrawal by subject	
Adverse event	0
Related to COVID-19	0
Not related to COVID-19	0
Study procedure	0
Othera	0
Related to COVID-19	0
Not related to COVID-19	0
Reason for study discontinuation	
Poor compliance to protocol	0
Withdrawal by subject	0

Site terminated by sponsor	0
Study terminated by sponsor	0
Death	3 (8.6)
Otherb	0
Related to COVID-19	0
Not related to COVID-19	0
Status at last contact[n(%)]	
Alive	21 (60.0)
Dead	13 (37.1)

a Verbatim term for these discontinuations is provided in the listing of participants with permanent full study intervention discontinuation.

b Verbatim term for these discontinuations is provided in the listing of participants with study discontinuation.

Note: Permanent full study intervention discontinuation is defined as the discontinuation of all the study drugs of the combination. When all study drugs are not discontinued at the same time, the reason for permanent full discontinuation is the reason for discontinuation of the last study drug stopped.

Percentages are calculated using the number of participants enrolled and exposed as denominator.

PGM=PRODOPS/SAR408701/ACT16444/CSR_02/REPORT/PGM/dis_dispo_s_t.sas
OUT=REPORT/OUTPUT/dis_dispo_s_t_i.rtf (18DEC2024 9:02)

Diagnosis and criteria for inclusion:

Participants with histologically or cytologically confirmed metastatic or locally advanced unresectable disease, at least 1 radiologically measurable tumor lesion of location accessible to biopsy per clinical judgment of the treating physician, confirmed progression at baseline, and Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1 were eligible to enter the study.

Study products

Investigational medicinal product(s):

Tusamitamab ravtansine

Formulation/Form & composition: infusion

Route(s) of administration: intravenous (IV)

Ramucirumab

Formualation/Form & composition: infusion

Route(s) of administration: intravenous (IV)

Duration of treatment/participation:

The study duration for a participant included a screening period of up to 28 days, followed by a treatment period where enrolled participants received the study intervention until disease progression, an unacceptable adverse event (AE), death, the start of a new anticancer therapy, or a decision to stop treatment by the participant or Investigator. Treatment cycles lasted 2 Weeks. After stopping the intervention, participants had an end-of-treatment assessment within 30 days of the last investigational manufacturing product (IMP) dose or before starting another anticancer therapy. A safety follow-up visit occurred about 90 days after the final IMP dose, unless any related adverse events resolved or stabilized, in which case no further visits were required.

Statistical methods: Information regarding planned analysis for the study is mentioned in the statistical analysis plan.

Results summary:

Demographic and other baseline characteristics

The majority of the participants were male and had an ECOG performance status of 1. The median age of participants was 64 years (range: 43 to 81 years). Approximately half of the participants were less than 65 years of age. All but except 1 participant with had metastatic disease.

Exposure

The median relative dose intensities of tusamitamab ravtansine and ramucirumab were 88.50% (range: 42.3% to 104.4%)] and 93.30% (range: 39.4% to 108.9%), respectively. Overall, the median number of cycles per participant was 5.0 (range: 1 cycle to 43 cycles). The median duration of IMP exposure was 13.14 weeks (range: 2.0 to 116.0 weeks). Forty percent of participants (N=14) had at least 18 weeks of exposure to the study treatment. Additional exposure since the abbreviated CSR corresponded to 22 cycles of tusamitamab ravtansine and ramucirumab, administrated to the 2 participants who were under intervention at the time of the abbreviated CSR.

Efficacy

Best Overall Response:

Five participants of 35 participants (14.3%) had confirmed partial response (PR), none of the participants had confirmed complete response (CR), and 17 participants (48.6%) had stable disease (SD) as best overall response (BOR) per Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1) criteria. The objective response rate (ORR) was 14.3% (95% confidence interval [CI]: 4.8% to 30.3%), and the disease control rate (DCR) was 62.9% (95% CI: 44.9% to 78.5%) in the All-treated population. In the Activity population, ORR was 15.2% and DCR was 66.7%. All 5 confirmed PR occurred in participants with CEACAM5 expression ≥80% of >2+ in tumor cells.

Progression-free Survival

Thirty-two participants (91.4%) had progression free survival (PFS) events, and 3 participants (8.6%) did not have any PFS event (were censored). The Kaplan-Meir estimated median PFS was 3.78 months (95% CI: 1.5 months to 5.8 months). The PFS probability for participant survival without progression was reduced over a time period of 2 to 12 months.

Safety results:

- Overall, all 35 participants experienced at least 1 treatment-emergent adverse event (TEAE); of these, 23 participants (65.7%) experienced Grade ≥3 TEAEs. Treatment-emergent serious adverse events (SAEs) were reported in 15 participants (42.9%). The TEAEs (any grade) considered by the Investigator as related to IMP were reported in 28 participants, and 11 of 28 participants (31.4%) had Grade ≥3 related TEAEs. Three participants (8.6%) had Grade 5 TEAEs. Five participants (14.3%) had TEAEs that resulted in IMP discontinuation during the study. Since the cut-off date of the abbreviated CSR, except 1 participant (2.9%) who had a TEAE leading to permanent partial discontinuation of ramucirumab, the overview of TEAEs is unchanged.

- Thirteen deaths [37.1%] were reported, 3 deaths (8.6%) during the treatment period and 10 deaths (28.6%) post-treatment period. Out of 13 deaths, 8 deaths (22.9%) were due to disease progression (1 death [2.9%] occurred during the treatment period and 7 deaths [20.0%] occurred during the post-treatment period), and 5 deaths were due to other reasons. The 3 deaths during the treatment period were associated with Grade 5 TEAEs coding to the preferred terms (PTs): Death (2 participants; 5.7%) and Malignant neoplasm progression (1 participant; 2.9%). These Grade 5 TEAEs were assessed as not related to either tusamitamab ravtansine nor ramucirumab.
- Of the 15 participants (42.9%) reporting treatment-emergent SAEs, 13 participants (37.1%) reported Grade ≥3 events. Three participants (8.6%) had treatment-emergent SAEs related to IMP; 1 participant (2.9%) had pyrexia (system organ class [SOC]: General disorders and administration site conditions), 1 participant (2.9%) had diarrhoea (SOC: Gastrointestinal disorders), and 1 participant (2.9%) had alanine aminotransferase (ALT) increased and aspartate aminotransferase (AST) increased (SOC: Investigations). All the events except pyrexia were Grade ≥3. The events of diarrhoea, ALT increased, and AST increased were related to tusamitamab ravtansine, and the event of pyrexia was related to ramucirumab.
- Five participants (14.3%) had the following TEAEs leading to permanent full IMP discontinuation: pneumonia, thrombocytopenia, and upper gastrointestinal hemorrhage (1 participant [2.9%] each), and death (2 participants; 5.7%). All the TEAEs leading to IMP discontinuation were Grade ≥3 events and not related to IMP.
- Nineteen participants (54.3%) had TEAEs leading to dose modification of tusamitamab ravtansine, and 7 of these participants (20.0%) had Grade ≥3 events. Seventeen participants (48.6%) had TEAEs leading to dose modification of ramucirumab, including 9 participants (25.7%) who had Grade ≥3 events.
- No DLT was reported in the study. Four participants were reported with adverse events of special interest (AESIs). One participant had AESIs (PT: ALT increased, and AST increased) which were serious, and related to IMP. The event of ALT increased was not resolved but the severity was reduced to Grade 2, and the event of AST increased was resolved.
- Ten participants (28.6%) had treatment-emergent corneal events; none of the events were ≥Grade 3, serious, or led IMP discontinuation.
- One participant (2.9%) had atrioventricular block second degree, and it was not a ≥Grade 3 event.
- Five participants (14.3%) had peripheral neuropathy events, and none of the events were ≥Grade 3.
- Twenty-two participants (62.9%) had gastrointestinal disorder events, and 6 participants had ≥Grade 3 events.
- Nine participants (25.7%) had hepatic disorder events, and 2 participants had ≥Grade 3 events.

Biomarker results

Out of 246 participants tested for CEACAM5 expression, 32.5% had high CEACAM5 expressors. A total of 19.1% of pre-screened participants had a CEACAM5 expression in ≥80% of tumor cells with 2+/3+ intensity. The median level of circulating CEA for prescreened participants before IMP administration was higher in CEACAM5 high expressors (7.10 µg/L) as compared to CEACAM5 nonexpressers and moderate expressers (3.95 µg/L and 3.60 µg/L, respectively). There was a weak correlation between circulating CEA at pre-screening and CEACAM5 H-score (Spearman's rank-order correlation coefficient of 0.26). There was a strong correlation between pre-screening and screening circulating CEA (Spearman's rank-order correlation coefficient of 0.94; intraclass correlation coefficient [90% CI]: 0.81 [0.7, 0.9]).

Of 24 participants with circulating CEA levels <50µg/L, 4 participants (16.7%; 95% CI: 4.74% to 37.4%) had objective responses. Of 9 participants with circulating CEA levels ≥100µg/L, 1 participant (11.1%) had an objective response.

Other results

A total of 31 participants from the all-treated population had at least 1 post-baseline anti-therapeutic antibodies (ATA) result (ATA population). Out of 31 participants, 4 participants (13.8%) had treatment-emergent ATA (all 4 participants had treatment-induced ATA and no participant had treatment-boosted ATA). The median time to onset of ATA response was 1.9 months (range: 0.8 to 2.8 months).

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