Sponsor: Sanofi **Drug substance(s):** SAR408701 - tusamitamab ravtansine	**Study Identifiers:** IND: 144484 EudraCT: 2019-003914-15 NCT: NCT04394624 WHO: U1111-1244-1585 **Study code:** ACT16525

Title of the study:

Open-label, single-arm trial to evaluate antitumor activity, safety, and pharmacokinetics of tusamitamab ravtansine (SAR408701) used in combination with ramucirumab or ramucirumab and pembrolizumab in metastatic, non-squamous, non-small-cell lung cancer (NSQ NSCLC) patients with CEACAM5-positive tumors, previously treated with platinum-based chemotherapy and an immune checkpoint inhibitor

Study center(s):

This study was conducted at 10 centers that enrolled participants from Czech Republic, Spain, Republic of Korea, Portugal, and United States.

Study period:

Date first study participant enrolled: 29 October 2020

Date last study participant completed: 24 October 2024

Study Status: The study was terminated due to the discontinuation of the overall development of tusamitamab ravtansine (SAR408701) by the Sponsor on 20 December 2023.

Phase of development: Phase 2

Objectives:

The below listed objectives for the doublet cohort are described in this report. The triplet cohort was planned in the study. However, due to early termination of the study program by the Sponsor, no participants were enrolled in the triplet cohort. Hence, the objectives for the triplet cohort are not listed below.

The primary objective for part 1 was to assess the tolerability and to confirm the recommended dose of tusamitamab ravtansine in combination with ramucirumab in the NSQ NSCLC population.

The primary objective for part 2 was to assess the antitumor activity of tusamitamab ravtansine in combination with ramucirumab in the NSQ NSCLC population.

The key secondary objectives were to assess safety and tolerability, durability of response, antitumor activity of tusamitamab ravtansine in combination with ramucirumab.

Methodology:

This was a Phase 2, open-label, single-arm, 2 cohort, multi-center study designed to assess safety, efficacy (antitumor activity), and pharmacokinetic (PK) of the combination of tusamitamab ravtansine and ramucirumab (doublet cohort), and tusamitamab ravtansine, ramucirumab, and pembrolizumab (triplet cohort).

The study was planned with a doublet cohort and a triplet cohort to assess the tolerability of the combinations of 2 and 3 study interventions, respectively. The doublet cohort was planned with 2 parts (Part 1 and Par 2), and the triplet cohort was planned with 1 part. Participants were enrolled to the doublet cohort, but no participants were enrolled in the triplet cohort due to the early termination of the study due to discontinuation of overall development program of CEACAM-5 (SAR439859) by the Sponsor on 20 December 2023. However, 1 participant who was benefiting from study intervention at the time of the development program discontinuation was allowed to continue receiving the study intervention.

For the participants still receiving study intervention at the time of the synoptic CSR, only study intervention data and safety data were collected. All serious adverse events (SAEs) related adverse events (AEs), and adverse events of special interest (AESIs) (with associated laboratory abnormalities, concomitant medications, and procedures, when applicable) continued to be collected. After intervention discontinuation, ongoing SAEs and related AE/AESI were to be followed until resolution or stabilization.

Doublet cohort

In Part 1 (Safety Run-in), the first 3 participants received ramucirumab at 8 mg/kg followed by tusamitamab ravtansine 100 mg/m2 every 2 weeks. There was a minimum delay of 1 week between the initial dosing of the first participant and the subsequent 2 participants treated at the same dose level. If ≤1/3 participants at the starting dose had a DLT, 3 additional participants were to be treated to confirm the tolerability of the combination. If ≤1/6 participants treated at the starting dose experienced a DLT, the starting dose was to be declared the recommended Phase 2 dose (RP2D). If ≥2/6 participants experienced a DLT, the dose of tusamitamab ravtansine was de-escalated to 80 mg/m2 every 2 weeks.

In Part 2, up to 36 participants, including 6 participants from Part 1 at the RP2D were planned to be evaluated for response.

Number of study participants:

In the doublet cohort, approximately 225 participants were planned to be prescreened to achieve up to 36 treated participants.

In the doublet cohort, 331 participants were prescreened with 37 participants screened further. Out of 37 participants, 6 were screen failures and 31 participants were enrolled (Enrolled population) and exposed to the study intervention (All-treated population). All 31 participants were included under the activity, PK, and anti-therapeutic antibody (ATA) populations. The DLT-evaluable population contained 6 participants. One participant (3.2%) was still ongoing at the time of the study cut-off date. The primary reason for full study intervention discontinuation was progressive disease (24 participants [77.4%]) followed by AEs not related to COVID-19 (6 participants [19.4%]). One participant (3.2%) discontinued due to other reasons (not related to COVID-19). During the study, 8 participants (25.8%) had critical or major protocol deviations.

Regarding study discontinuation, 5 participants (16.1%) withdrew from the study, and 1 participant (3.2%) discontinued due to study termination by the sponsor. The status (alive or deceased) of the remaining participants at the last contact is not provided in the given data.

Participant disposition - All-treated population

	Tusa rav 100 mg/m² + ramucirumab (N=31)
Enrolled and not exposed	0
Enrolled and exposed[n(%)]	31 (100)
Ongoing study intervention	0
Permanent full study intervention discontinuation	31 (100)
Reason for permanent full study intervention discontinuation	
Adverse event	6 (19.4)
Related to COVID-19	0
Not related to COVID-19	6 (19.4)
Progressive disease	24 (77.4)
Poor compliance to protocol	0
Withdrawal by subject	0
Other[a]	1 (3.2)
Related to COVID-19	0
Not related to COVID-19	1 (3.2)
Reason for study intervention withdrawal by subject	
Adverse event	0
Related to COVID-19	0
Not related to COVID-19	0
Study procedure	0
Other[a]	0
Related to COVID-19	0
Not related to COVID-19	0
Reason for study discontinuation	
Poor compliance to protocol	0
Withdrawal by subject	5 (16.1)
Site terminated by sponsor	0
Study terminated by sponsor	1 (3.2)
Other[b]	0
Related to COVID-19	0
Not related to COVID-19	0

[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.

Diagnosis and criteria for inclusion:

The inclusion criteria included participants aged ≥18 years, histological/cytological proven diagnoses of NSQ NSCLC, metastatic disease progression during/after platinum-based chemotherapy and immune checkpoint inhibitor, CEACAM5-positive (defined as CEACAM5 immunohistochemical [IHC] intensity ≥2+ in 50% of tumor cells) and provided the signed informed consent.

Study products

Investigational medicinal product(s):

Ramucirumab

Formulation/Form & composition: infusion

Route(s) of administration: intravenous (IV)

Tusamitamab ravtansine

Formulation/Form & composition: infusion

Route(s) of administration: IV

Pembrolizumab

Formulation/Form & composition: infusion

Route(s) of administration: IV

Duration of treatment/participation: The duration of study intervention was planned until the participant had clinical benefit or progressive disease or unacceptable toxicity or withdrawal of consent. Each cycle of study intervention had a duration of 2 weeks in the doublet cohort.

Criteria for evaluation:

Endpoints:

The primary endpoint for part 1 was to check the incidence of study intervention-related dose limited toxicity (DLT) at Cycle 1 and Cycle 2.

The primary endpoint for part 2 was evaluated by identifying objective response rate (ORR) as determined per response evaluation criteria in solid tumors (RECIST) v1.1.

The safety objective was evaluated by assessing the incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and laboratory abnormalities according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) V5.0. The durability and antitumor activity were evaluated by measuring the duration of response (DOR), disease control rate (DCR) as per RECIST 1.1, and progression-free survival (PFS).

Statistical methods:

The primary objectives of doublet cohort were assessed as planned. However, due to the decision to stop the overall development program by the Sponsor the planned statistical analyses were changed and reduced before the database lock of the study. Only relevant descriptive statistics and statistical modeling (participants disposition, demography, disease characteristics, deviations, best overall response, PK, Biomarker, exposure, and AEs) were analyzed.

Summary Results:

Demographic and other baseline characteristics:

The mean (standard deviation [SD]) age was 62.7 (10.1) years, with 19 participants (61.3%) aged <65 years. There were comparable proportions of male (48.4%) and female (51.6%) participants in the study. Thirteen participants (41.9%) were Asians. Majority of the participants (21 participants [67.7%]) had an eastern cooperative oncology group (ECOG) performance status score of '1'. The mean BSA (SD) was 1.709 (0.225) m^2.

All the participants were diagnosed with adenocarcinoma except 1 participant who was diagnosed with bronchioloalveolar carcinoma. The median time to initial diagnosis to first administration of the study intervention was 1.89 years (range: 0.4 to 12.1). Most of the participants (80.6%, 25 participants) had stage IV of the disease at diagnosis. The primary tumor location was right lung (20 participants [64.5%]), and 10 participants [32.3%] had ≥4 organs involved (including primary tumor location). Metastatic involvement in more than 50% of the participants included lungs (26 participants [83.9%]) or lymph nodes (19 participants [61.3%]).

Two participants (6.5%) were current smokers, with mean (SD) of 38.2 (32.0) smoking pack-years. The programmed death-ligand 1 (PD-L1) expression was ≥1% in 18 participants (58.1%). A total of 18 participants (58.1%) had CEACAM5 expression as per IHC in ≥80% of tumor cells. At baseline, the mean (SD) levels of circulating carcinoembryonic antigen (CEA) were 4588.03 (15217.44) µg/L; 24 participants (77.4%) had ≥5 µg/L level of circulating CEA, and 14 participants (45.2%) had ≥100 µg/L level of circulating CEA.

Most of the participants had taken 1 or 2 prior anticancer regimens in the advanced setting (17 participants [54.8%] and 8 participants [25.8%], respectively). Thirty participants (96.8%) received previous anti-PD-L1 therapy. A total of 15 participants (48.4%) had at least 1 prior course of radiotherapy related to cancer, and the mean (SD) time from the last dose of radiotherapy to first administration of investigational medicinal product (IMP) was 0.80 years (0.84). Nine participants (29%) had at least 1 prior surgery related to cancer. The mean (SD) time from the last dose of surgery to first administration of IMP was 3.22 years (2.85).

Exposure:

Overall, the median number of cycles per participant was 12 (range: 2.0 to 57.0), and the median duration of overall exposure was 24.14 weeks (range: 3.9 to 129.9). More than 10% of the participants had at least 78 weeks of overall exposure to the study intervention.

The median relative dose intensity (RDI), defined as the ratio of the dose intensity delivered to the protocol-specified dose intensity, for tusamitamab ravtansine was 90.0% and for ramucirumab was 94.7%. The median number of tusamitamab ravtansine cycles per participant was 11 (range: 2.0 to 57.0) and median number of ramucirumab cycles was 12 (range: 2.0 to 57.0).

Tusamitamab ravtansine dose delays within cycles occurred in 18 participants (58.1%), dose reductions occurred in 8 participants (25.8%), and dose omissions occurred in 7 participants (22.6%). No dose interruptions occurred. A total of 73 cycles (16.7%) had dose delays, 12 cycles (2.8%) had dose omissions, and 8 cycles (1.8%) had dose reductions.

Ramucirumab dose delays within cycles occurred in 19 participants (61.3%), dose reductions occurred in 3 participants (9.7%), dose omissions occurred in 2 participants (6.5%), and dose interruption occurred in 1 participant (3.2%). A total of 59 cycles (14.8%) had dose delays, 5 cycles (1.3%) had dose reductions, 8 cycles (2%) had dose omissions, and 1 cycle (0.3%) had dose interruption.

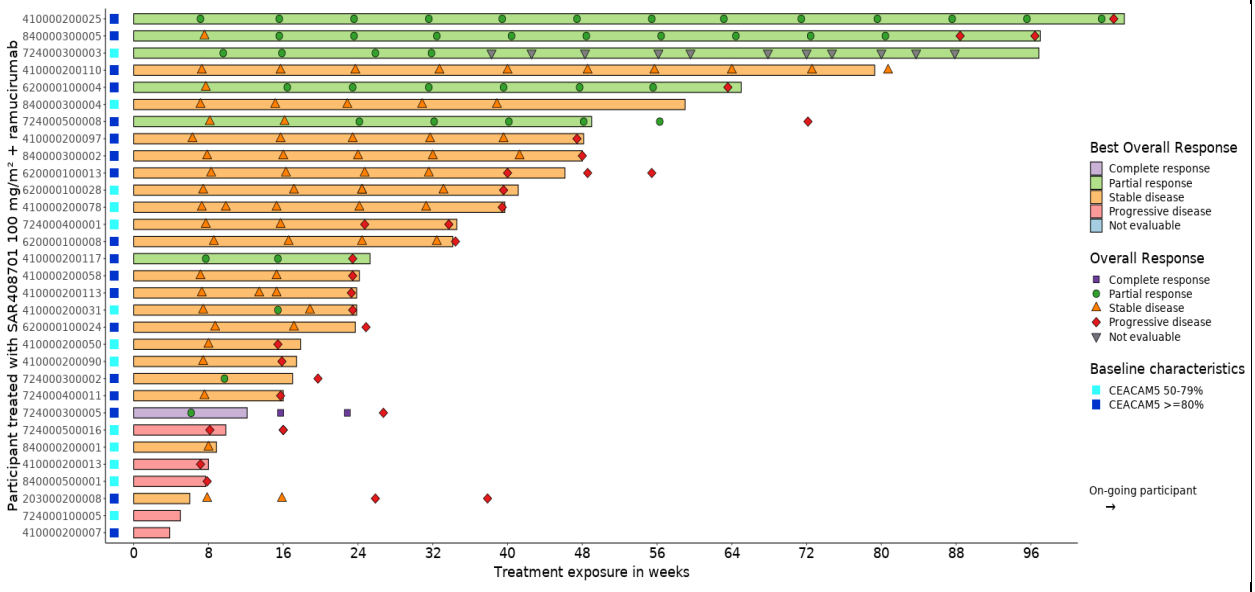
Efficacy and immunogenicity results:

Summary of best overall response and objective response rate as per RECIST 1.1 with confirmation of response by investigator - All-treated population

	Tusa rav 100 mg/m² + ramucirumab (N=31)
Best Overall Response [n (%)]	
Number	31
Complete Response	1 (3.2)
Partial Response	6 (19.4)
Stable Disease	19 (61.3)
Unconfirmed partial response	2 (6.5)
Progressive Disease	5 (16.1)
Objective Response Rate (confirmed CR and PR)	7 (22.6)
95%CI	9.59, 41.10
Disease Control Rate [n (%)]	26 (83.9)
95%CI	66.27, 94.55

CI: Confidence interval; CR: Complete response; PR: Partial response; RECIST: Response Evaluation Criteria in Solid Tumors

Swimmer plot of duration of study intervention, OR, and BOR - All-treated population



- Individual data show about half of the participants were treated for more than 6 months, whatever the CEACAM5 level at study entry.
- The Kaplan-Meir estimated median DOR was 11.1 months (95% CI: 3.5 months, not calculated).
- The Kaplan-Meir estimated median PFS was 6.0 months (95% CI: 5.4, 9.1).

- Of 31 participants, 4 participants (12.9%) had treatment-emergent ATA (all treatment-induced, no participant had treatment-boosted ATA). The median time to onset of ATA response was 4.2 months (range : 0.6, 11.7).

Safety results:

Overview of adverse event profile: Treatment-emergent adverse events - All-treated population

n (%)	Tusa rav 100 mg/m² + ramucirumab (N=31)
Participants with any TEAE	31 (100)
Participants with any grade ≥3 TEAE	13 (41.9)
Participants with any grade 5 TEAE	3 (9.7)
Participants with any treatment-emergent SAE	7 (22.6)
Participants with any treatment-emergent AESI	4 (12.9)
Participants with any TEAE leading to permanent full intervention discontinuation	5 (16.1)
Participants with any TEAE leading to permanent partial discontinuation of tusamitamab ravtansine	2 (6.5)
Participants with any TEAE leading to permanent partial discontinuation of ramucirumab	5 (16.1)
Participants with any TEAE related to IMP (any grade)	27 (87.1)
Participants with any grade ≥3 TEAE related to IMP	11 (35.5)
Participants with any treatment-emergent SAE related to IMP	2 (6.5)
Participants with any treatment-emergent corneal event	7 (22.6)
Participants with any ocular/visual symptoms TEAE	15 (48.4)
Participants with any treatment-emergent peripheral neuropathy event TEAE	11 (35.5)

IMP: Investigational medicinal product; TEAE: Treatment-emergent adverse event; SAE: Serious adverse event

- No DLTs were reported in part 1 of the study.

- The most frequently reported TEAEs (≥20% of participants) by PT were nausea (13 participants [41.9%]), hypertension, proteinuria (10 participants [32.3%] each), decreased appetite, diarrhea (9 participants [29.0%] each), arthralgia, asthenia (8 participants [25.8%] each), coronavirus 2019 (COVID-19), thrombocytopenia, headache, vision blurred, cough, and platelet count decreased (7 participants [22.6%] each).

- The most frequently reported ≥Grade 3 TEAEs in >5% of the participants were hypertension (4 participants [12.9%]), neutrophil count decreased, neutropenia, and gamma-glutamyl transferase (GGT) increased (2 participants [6.5%] each).

- Seven participants (22.6%) had 10 treatment-emergent SAEs; 1 participant each had SAEs (pneumonia, hemoptysis, confusional state, cutaneous T cell lymphoma, colitis ulcerative, pulmonary hemorrhage) and 1 participant had 4 SAEs (multiple organ dysfunction syndrome, hepatic function abnormal, renal impairment, and pleural effusion). With the exception of hemoptysis and colitis ulcerative, which were reported in 1 participant each, none of these SAEs were assessed by the investigator as having been related to the study intervention.

- Three deaths (9.7%) were reported during the treatment period; these included deaths in 2 participants (6.5%) due to disease progression, and in 1 participant (3.2%) due to an AE (pulmonary hemorrhage). Deaths in 10 participants (32.3%) were reported during the post-treatment period; these included deaths due to disease progression for 9 participants (29.0%) and death for 1 participant (3.2%) was classified as due to other cause.

- Of the 4 participants with treatment-emergent adverse event of special interests (AESIs); 2 participants (6.5%) had Grade 3 treatment-emergent corneal events (keratopathy and keratitis). No Grade 4 corneal events were reported. The corneal events in 6 participants were assessed by the investigator as having been related to the IMP. Of these, the corneal events in 5 participants (16.1%) had resolved by the time of data cut-off date.

- Two participants had treatment-emergent AESIs of gamma-glutamyl transferase (GGT) increased (1 participant had Grade 4 GGT increased, and 1 participant had Grade 3 GGT increased). These were assessed by the investigator as having been related to the IMP and 2 events of GGT increased had not resolved.

- No participants had Grade 3 ocular/visual events. The most frequently reported ocular/visual events in >5% of the participants were vision blurred (7 participants [22.6%]), cataract (5 participants [16.1%]), dry eye, eye pruritis, periorbital edema, and visual acuity reduced (2 participants [6.5% each]).

- No participants had cardiac conduction defects.

- No participants had Grade 3 peripheral neuropathy TEAEs. The most frequently reported peripheral neuropathy event in >5% of the participants was neuropathy peripheral and paresthesia (4 participants [12.9%] each).

- Twenty-two participants (71%) had GI disorder TEAEs. One participant (3.2%) had Grade ≥3 events (diarrhea and colitis ulcerative). The most frequently reported GI disorder TEAEs in >10% of participants were nausea (13 participants [41.9%]), diarrhea (9 participants [29%]), constipation (6 participants [19.4%]), and vomiting (5 participants [16.1%]).

- Three participants (9.7%) had hypersensitivity TEAEs (1 participant each had periorbital edema, rash pruritic, and face edema). None of the events were Grade ≥3.

- Nine participants (29%) had hepatic disorder TEAEs. Three participants (9.7%) had Grade ≥3 events (1 participant had hepatic function decreased, and 2 participants had GGT increased). More than 5% of the participants had alanine aminotransferase increased, aspartate aminotransferase increased (9.7% each), and GGT increased (6.5%).

- Twelve participants (38.7%) had hematological TEAEs. Of these, 4 participants (12.9%) had Grade ≥3 events.

- The following Grade ≥3 hematological/coagulation/clinical chemistry abnormalities were reported; 1 participant (3.2%) each had Grade 3 white blood cell count decreased, Grade 3 platelet count decreased, Grade 3 activated partial thromboplastin time prolonged, Grade 3 hypokalemia, Grade 3 creatinine increased, and Grade 4 neutrophil count decreased. Three participants (9.7%) each had Grade 3 neutrophil count decreased, Grade 3 lymphocyte count decreased, and Grade 3 hyponatremia. Elevated level of urine protein was observed as 2+ in 3 participants (9.7%), 3+ in 2 participants (6.5%), and 4+ in 1 participant (3.2%).

- Eight participants (25.8%) had heart rate >100 beats/min and increase from baseline ≥20 beats/min; 1 participant (3.2%) had PR interval 220 msec and increase from baseline ≥25%, and 1 participant (3.2%) had QRS interval >110 msec and increase from baseline ≥25%. No other major changes from baseline were reported for vital signs (systolic and diastolic blood pressure, temperature, and weight).

- No clinically meaningful difference in electrocardiogram evaluations were observed during the treatment period except one participant (3.2%) with QT-interval corrected using the Fridericia formula (QTcF) prolongation of >500 msec and 2 participants (6.5%) with QTcF value increase >60 msec from baseline (which were asymptomatic).
- No clinically meaningful differences in physical examination findings were observed during the treatment period.

Issue date: 13-Oct-2025