Sponsor: Sanofi **Drug substance(s):** SAR408701 - tusamitamab ravtansine	**Study Identifiers:** IND: 144484 EudraCT/EU trial number: 2020-003096-18 NCT: NCT04659603 WHO: U1111-1244-1644 **Study code:** ACT16432

Title of the study:

Open-label, multi-cohort, Phase 2 trial, evaluating the efficacy and safety of tusamitamab ravtansine (SAR408701) monotherapy and in combination in patients with CEACAM5 positive advanced solid tumors.

Study center(s):

This study was conducted at 19 centers that enrolled participants in 10 countries (Argentina, Chile, Hungary, Korea, Netherlands, Russia, Spain, Taiwan, Turkey, US).

Study period:

Date first study participant enrolled: 12/April/2021

Date last study participant completed: 16/Feb/2024 (data cut-off date)

Study Status: Terminated. Sponsor decision, the decision is not related to any safety concern.

Phase of development: Phase 2

Objectives and endpoints:

The primary objective of Cohort A, Cohort B, and Cohort C Part 2 was to assess the antitumor activity of tusamitamab ravtansine in mBC and tusamitamab ravtansine monotherapy and in combination with gemcitabine in mPAC as assessed by objective response rate (ORR) of tusamitamab ravtansine (proportion of participants who have a confirmed complete response [CR] or partial response [PR] as per Response Evaluation Criteria in Solid Tumors [RECIST] v1.1).

The primary objective of Cohort C Part 1 was to confirm of the recommended tusamitamab ravtansine dose when administered in combination with gemcitabine based on incidence of dose limiting toxicities (DLTs) in the 28 Day DLT observation period (Cycle 1).

Secondary objectives were to assess the safety and tolerability of tusamitamab ravtansine administered as monotherapy and in combination with gemcitabine as assessed by treatment-emergent adverse events (TEAEs), serious adverse events (SAEs) and laboratory abnormalities; to evaluate progression-free survival; to evaluate disease control rate (percentage of participants with confirmed CR or PR or stable disease); to evaluate duration of response; to evaluate the pharmacokinetic (PK) of tusamitamab ravtansine and gemcitabine when given in combination, and to assess the immunogenicity of tusamitamab ravtansine.

Methodology:

This was a Phase 2, open-label, multi-cohort, multi-center study assessing efficacy (anti-tumor activity), safety, and immunogenicity of tusamitamab ravtansine single agent in participants with metastatic breast cancer (mBC) (Cohort A) and metastatic pancreatic adenocarcinoma (mPAC) (Cohort B) with carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5)-positive tumors (defined as CEACAM5 IHC intensity ≥2+ in ≥50% of tumor cells), and also assessing efficacy (antitumor activity), safety, tolerability, pharmacokinetics, and immunogenicity of tusamitamab ravtansine combined with gemcitabine in participants with mPAC (Cohort C) with CEACAM5 positive tumors. During the prescreening phase, participant's tumor samples were collected to evaluate

CEACAM5 status (central assessment by IHC). Only participants with mBC and mPAC determined to be CEACAM5-positive went through protocol screening. After being screened, the eligible participants received tusamitamab ravtansine as single agent treatment (Cohorts A and B) or in combination with gemcitabine (Cohort C) until documented disease progression, unacceptable toxicity, new anticancer therapy initiation, or the participant's or Investigator's decision to stop the treatment.

In Cohorts A and B, participants received a tusamitamab ravtansine loading dose at 170 mg/m² on Day 1 of Cycle 1, followed by 100 mg/m² every 2 weeks (Q2W) from Cycle 2 and in all other cycles. In Cohort C, each treatment cycle was 28 days (4 weeks). Cohort C comprised 2 parts:

Part 1 (Safety Run-In): In Part 1, participants received a tusamitamab ravtansine loading dose at 170 mg/m² on Day 1, followed by 100 mg/m² Q2W; participants also received gemcitabine 1000 mg/m2 on Day 1, Day 8, and Day 15 every 4 weeks (Q4W).

Table 1 - Dose levels for Part 1 (safety run-in)

Dose level (DL)	Tusamitamab ravtansine	Gemcitabine
Starting dose	170 mg/m^2 on D1; 100 mg/m2 Q2W thereafter	1000 mg/m^2 on D1, D8, and D15 Q4W
Minus -1 (DL-1)	135 mg/m^2 on D1; 100 mg/m2 Q2W thereafter	1000 mg/m^2 on D1, D8, and D15 Q4W

BSA = body surface area; DL-1 = dose level -1; Q2W = every 2 weeks; Q4W = every 4 weeks; D = day.

For participants with a BSA >2.2 m2, the tusamitamab ravtansine dose will be calculated based on a BSA of 2.2 m2.

In Part 2 of Cohort C, the recommended dose confirmed in Part 1 was planned to be evaluated for activity in 24 to 27 additional participants. A total of 16 participants were evaluated for activity.

Number of study participants:

Planned: A total of 118 participants were planned for the study.

Enrolled/Randomized: A total of 55 participants were screened (mBC Cohort A: 6, mPAC Cohort B: 32, mPAC Cohort C: 17) of whom 50 participants (mBC Cohort A: 6, mPAC Cohort B: 28, mPAC Cohort C: 16) were enrolled and treated in the study.

Diagnosis and criteria for inclusion:

Participants with evidence of metastatic disease (histological or cytologic diagnosis of breast cancer for participants with mBC and confirmed diagnosis of pancreatic ductal adenocarcinoma). Participants with at least 1 measurable lesion that had not been irradiated were eligible for the study. Participants had to have eastern cooperative oncology group performance status 0 to 1, CEACAM5-positive tumors. Participants with mBC had to have prior therapy with 2 to 4 prior cytotoxic chemotherapy regimens for non-triple-negative breast cancer (TNBC) tumors or 1 to 4 regimens for TNBC tumors. Participants with mPAC had documented radiographic progression or documented intolerance after 1 or 2 prior systemic chemotherapy lines and had documented radiographic progression or documented intolerance after 1st line fluoropyrimidine-containing chemotherapy.

Study products

Investigational medicinal product(s):

Tusamitamab ravtansine

Formulation/Form & composition: concentrated solution for IV (intravenous)

Route(s) of administration: IV infusion

Gemcitabine

Formulation/Form & composition: lyophilized powder

Route(s) of administration: IV infusion

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 documented disease progression, unacceptable toxicity, new anticancer therapy initiation, or the participant's or Investigator's decision to stop the treatment. Treatment cycles lasted 2 Weeks for Cohort A and B and 4 Weeks for Cohort C. After stopping the intervention, participants had an end-of-treatment assessment 30 days after the last investigational medicinal product (IMP) administration or before starting another anticancer therapy. A safety follow-up visit occurred about 90 days after the last IMP administration, unless any related adverse events (AEs)/serious adverse events (SAEs)/adverse events of special interest (AESIs) 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.

Summary Results:

Population characteristics:

Demographic and other baseline characteristics:

Six participants with mBC and 44 participants with mPAC (28 in Cohort B and 16 in Cohort C) were enrolled and treated in the study. The median age of participants in mBC, in mPAC Cohort B, and mPAC Cohort C was 46.5 years, 65 years, and 63.5 years, respectively. All 6 participants in mBC Cohort A were aged <65 years and were female. Half of the participants in both Cohort B and Cohort C aged <65 years. Most of the participants in mPAC Cohort B were female and the proportions of male and female participants in mPAC Cohort C were comparable. All participants had metastatic and measurable disease.

Exposure:

Five participants (83.3%) with mBC had at least 12 weeks of overall exposure to the study treatment. Three participants (10.7%) in mPAC Cohort B had at least 36 weeks (9 months) of overall exposure to the study treatment. Six participants (37.5%) had at least 24 weeks (6 months) and 2 participants (12.5%) had at least 36 weeks (9 months) of overall exposure to tusamitamab ravtansine. Five participants (31.3%) had at least 24 weeks, and 2 participants (12.5%) had at least 36 weeks of overall exposure to gemcitabine.

Efficacy results:

- mBC Cohort A: None of the 6 participants had confirmed CR or PR, and 4 participants had stable disease as BOR as per RECIST v1.1 criteria. The disease control rate (CR+PR+SD) was 66.7% (95% CI: 22.28, 95.67).
- mPAC Cohort B: The ORR (CR+PR) was 3.6% (95% CI: 0.09, 18.35). The Kaplan-Meier estimated median progression-free survival and duration of response was 1.87 months (95% CI: 1.643, 2.267) and 4.11 months (95% CI: NC), respectively. The DCR (CR+PR+SD) was 28.6% (95% CI: 13.22, 48.67).

- mPAC Cohort C: The ORR (CR+PR) was 31.3% (95% CI: 11.02, 58.66). The Kaplan-Meier estimated median PFS and DOR was 4.73 months (95% CI: 1.873, NC) and 7.26 months (95% CI: 3.713, NC), respectively. The DCR (CR+PR+SD) was 75.0% (95% CI: 47.62, 92.73).

Safety results:

- mBC Cohort A: All 6 participants experienced at least 1 TEAE including 4 participants (66.7%) who experienced Grade ≥3 TEAEs. The most frequently reported TEAEs PTs were nausea (3 participants [50%]), stomatitis, tumour pain, and vomiting (2 participants each [33.3%]). None of the participants had serious TEAEs or TEAEs leading to permanent intervention discontinuation. Four participants (66.7%) died during the posttreatment period due to disease progression and no deaths were reported during the treatment period. Two participants had treatment-emergent corneal events and 1 participant had peripheral neuropathy events.
- mPAC Cohort B: All 28 participants in experienced at least 1 TEAE including 18 participants (64.3%) who experienced Grade ≥3 TEAEs. Three participants (10.7%) had Grade 5 TEAEs. The most frequently reported TEAEs PTs were asthenia (46.4% of participants), decreased appetite (32.1% of participants), abdominal pain (25% of participants), and disease progression (21.4% of participants). Serious TEAEs were reported in 16 participants (57.1%) including 1 participant with related serious TEAE (gastritis erosive). Twenty-one participants (75%) died during the treatment period (3 participants [10.7%]) or posttreatment period (18 participants [64.3%]). All 3 deaths during the treatment period and 16 deaths during the posttreatment period occurred due to disease progression, and 2 deaths during the posttreatment period occurred due to unknown causes. Eight participants (28.6%) had treatment-emergent corneal events, and 3 participants (10.7%) had peripheral neuropathy events.
- mPAC Cohort C: No DLTs were reported during safety run-in period. All 16 participants experienced at least 1 TEAE; including 12 participants (75%) who experienced Grade ≥3 TEAEs. Four participants (18.8%) had Grade 5 TEAEs. The most frequently reported TEAEs (all grades, ≥25% of participants) by primary SOC were gastrointestinal disorders (75% of participants), general disorders and administration site conditions (62.5% of participants), infections and infestations (50.0% of participants) eye disorders, investigations, and nervous system disorders (43.8% of participants each), blood and lymphatic system disorders, and metabolism and nutrition disorders (37.5% of participants each), muscoskeletal and connective tissue disorders (31.3%), skin and subcutaneous tissue disorders (25% of participants). The most frequently reported TEAEs PTs were decreased appetite (31.3% of participants), fatigue, back pain, constipation, dry eye, anaemia, and thrombocytopenia (25% of participants each). Serious TEAEs were reported in 8 participants (50%) including 1 participant who had treatment related serious TEAEs (urinary tract infection). Four participants (25%%) died during the treatment period and 5 participants (31.1%) died during the posttreatment period that were all due to disease progression. Two participants (12.5%) had treatment-emergent corneal events, and 6 participants (37.5%) had peripheral neuropathy events.

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