AMENDED CLINICAL TRIAL PROTOCOL 02

Protocol title:	**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**
Protocol number:	**ACT16432**
Amendment number:	**02**
Compound number (INN/Trademark):	**SAR408701 tusamitamab ravtansine/Not applicable**
Brief title:	**Tusamitamab ravtansine monotherapy and in combination in patients with CEACAM5-positive advanced solid tumors (CARMEN-BT01)**
Study phase:	**Phase 2**
Sponsor name:	**Sanofi aventis recherche & développement**
Legal registered address:	**1 avenue Pierre Brossolette, 91380 Chilly- Mazarin, FRANCE**
Monitoring team's representative name and contact information	

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Date: 25-Jul-2022 Total number of pages: 127

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial protocol 02	All	Date: 25-Jul-2022, version 1 (electronic 3.0)
Amended Clinical Trial protocol 01	All	Date: 01-Oct-2021, version 1 (electronic 1.0)
Original Protocol		Date: 23-Sep-2020, version 1 (electronic 1.0)

AMENDMENT 02 (25 July 2022)

This amended protocol 02 (amendment 02) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The purpose of this amendment is to add a new cohort (Cohort C) to evaluate tusamitamab ravtansine, an anti-CEACAM5 antibody-drug conjugate [ADC] containing the cytotoxic antitubulin agent DM4, in combination with gemcitabine in participants with pancreatic adenocarcinoma (mPAC).

Additionally, the interim analysis for the metastatic breast cancer (mBC) Cohort A has been removed, as enrollment has been stopped due to the low prevalence of CEACAM5-positive tumors in participants with mBC (3.9%, compared to the expected 10% to 15%). Modifications to protocol wording were implemented as detailed in the following table.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Cover page	Modified title and abbreviated title	To reflect addition of new combination cohort
1.1 Synopsis, rationale, 1.2 Schema	Added clarifications for Cohorts A and B, and added Cohort C	To reflect study design change
1.1 Synopsis, Objectives and endpoints; 3 Objectives and endpoints	Added objectives and endpoints of Cohort C	To reflect new cohort
1.1 Synopsis, Overall design; 4.1 Overall design	Added overall study design of Cohort C, including numbers of participants to be prescreened, screened, treated, and evaluable; new Figure 2 for Cohort C dose escalation	To reflect new cohort design
1.1 Synopsis, study intervention; 1.2 Schema, 6.1 Study intervention(s) administered	Added gemcitabine to the interventions	To reflect Cohort C of combination treatment

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis, study intervention; 6.1 Study intervention(s) administered	Added reference to guidelines for antiemetic premedication	To provide complete information for gemcitabine intervention
1.1 Synopsis, 1.2 Schema, 9.1 Sample size determination	Updated calculated sample sizes	To reflect additional participants to be enrolled in Cohort C
1.1 Synopsis, 9.2 Populations for analyses	Added definitions of DLT-evaluable population and PK population	To define populations for analysis of primary endpoint (DLT) in Cohort C Part 1, and new PK analyses for Cohort C
1.1 Synopsis, 9.3.2 Primary endpoint(s)	Added paragraph describing primary endpoint for Part 1 of Cohort C	To specify DLTs as new primary endpoint for Part 1 of Cohort C
1.3.2 Study procedures flowchart for Cohort C	Added new flowchart	To reflect study procedures for Cohort C
1.3.3 PK/ATA flow charts for tusamitamab ravtansine and gemcitabine samples for Cohort C	Added new sampling schedules	To reflect PK analysis of combination treatment and immunogenicity of tusamitamab ravtansine for Cohort C
2.1 Study rationale	Added rationale for Cohort C	To reflect study rationale for Cohort C
2.2 Background	Added background for combination treatment	To reflect background for Cohort C
2.3 Benefit/risk assessment	Added benefit/risk assessment for gemcitabine and combination	To reflect study design change
4.2 Scientific rationale for study design, 9.3.1 General considerations, 9.4 Interim analyses	Removed mention of interim analysis for Cohort A	The mBC cohort stopped enrollment
4.2 Scientific rationale for study design, 9.3.1 General considerations, 9.4 Interim analyses	Added interim analysis for Cohort C	To describe process for deciding to continue enrolling new Cohort C
4.2 Scientific rationale for study design	Updated scientific rationale	To reflect new cohort
5.1 Inclusion criteria, I 12	Specified Cohort B for inclusion criterion 12	To distinguish from criterion for Cohort C
5.1 Inclusion criteria I 13	Added requirement for contraceptive use “at least 6 months after the last dose of gemcitabine” for all male participants	In accordance with male contraception guidance for chemotherapy
5.1 Inclusion criteria, new I 15	Added prior fluoropyrimidine containing chemotherapy requirement for Cohort C	To define appropriate patient population for new combination treatment cohort
5.2 Exclusion criteria, new E 27	Added exclusion of participants with previous systemic taxane or gemcitabine treatment from Cohort C	To define appropriate patient population for new combination treatment cohort
6.1 Study intervention(s) administered	Added gemcitabine to the interventions	To reflect Cohort C of combination treatment
6.5.1 Determination of recommended dose for Cohort C	New section added to describe recommended dose determination for gemcitabine combination treatment	To reflect Cohort C dose selection scenario

Section # and Name	Description of Change	Brief Rationale
6.5.2 Individual dose adjustment/dose delay: Cohort A, Cohort B and Cohort C Part 2	Added rules for individual dose modification in text and additional row in Table 9 describing dose reduction of gemcitabine for participants receiving combination treatment	To clarify dose modification for participants in the combination treatment cohort
6.5.3 Retreatment criteria	Added retreatment criteria for Day 8 and Day 15	To specify retreatment criteria for gemcitabine
8.3.8 Adverse event of special interest	Added dose-limiting toxicity (DLT) to list of adverse events of special interest (AESI)	To report of DLT events as AESI
8.3.10 Guidelines for managing specific adverse events	Added guidelines for managing specific adverse events of gemcitabine	To reflect Cohort C of combination treatment
8.4 Pharmacokinetics	Added new section	To reflect PK analysis of Cohort C of combination treatment
8.6.2 Other biomarkers	Specified Cohort A and Cohort B for DNA analyses	To clarify that circulating tumor DNA analysis will not be assessed for Cohort C
8.6.2 Other biomarkers	Added pre-infusion IgG sample at Cycle 1	To explore the impact of IgG on PK parameters
9.3.1 General considerations	Described gemcitabine combination regimen for Cohort C	To reflect new cohort design
9.3.3 Secondary endpoint(s)	Added PK analysis to secondary endpoint analyses	To reflect PK analysis for Cohort C (gemcitabine combination treatment)
10.1.5 Committee structure	Added study committee in Cohort C Part 1	To confirm the recommended tusamitamab ravtansine dose when administered in combination with gemcitabine
10.6 Appendix 6: Recommended supportive care and/or dose modification guidelines for drug-related adverse events	Added dose modification for gemcitabine	To reflect addition of gemcitabine to tusamitamab in combination regimen in Cohort C
10.9 Appendix 9 Contingency measures for a regional or national emergency that is declared by a governmental agency: 10.9.4 Study procedures	Specified “for Cohorts A and B”	To clarify for which cohorts contingency measures may apply
10.10 Appendix 10	Updated list of strong CYP3A inhibitors	To provide current list drugs with potential for PK interaction
11 References	Added new references (Von Hoff et al, Hesketh et al, Mita et al)	Added references for Cohort C design and premedication for gemcitabine
throughout	typographical, grammatical, and style edits	Clarity and consistency

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol title:

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

Brief title:

Tusamitamab ravtansine monotherapy and in combination in patients with CEACAM5-positive advanced solid tumors

Rationale:

The carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5) is one of the 7 members of the CEACAM subgroup of a family of glycoproteins involved in cell adhesion (1). It was first described in 1965 as a tumor-associated antigen in human colon cancer tissue extracts (2). High levels of CEACAM5 expression have since been observed in several epithelial tumors, while in normal adults, its expression is limited to only a few tissues (1, 3). Immunostaining of CEACAM5 in a large panel of human tumor tissue microarray samples has shown the highest prevalence of cell surface CEACAM5 expression in adenocarcinoma of the colon and the stomach, and in its subtype signet ring cells as well as in non-squamous (NSQ) non-small-cell lung carcinoma (NSCLC).

Tusamitamab ravtansine is an antibody-drug conjugate (ADC) combining hu769_4D4 (SAR408377), a humanized antibody that recognizes selectively the A3-B3 extracellular domain of CEACAM5, with the potent cytotoxic maytansinoid derivative ravtansine (DM4), which inhibits microtubule assembly. Tusamitamab ravtansine is expected to selectively deliver DM4 to cancer cells expressing the CEACAM5 antigen.

In the first-in-human study TED13751, a cohort of heavily pretreated NSQ NSCLC patients with CEACAM5-positive tumor at the membrane (≥2+ in intensity involving at least 50% of the tumor cell population) have been treated with tusamitamab ravtansine at the recommended dose of 100 mg/m² every 2 weeks. The 64 treated patients showed encouraging anti-tumor activity and was associated with a response rate of 20.3% (95% confidence interval [CI]: 12.27%-31.71%); 28 (43.8%) had stable disease. Patients were heavily pretreated with a median of 3 prior treatments (1 to 10 lines) for advanced disease, including antitubulin agents (60.9%) and anti-programmed cell death protein 1 (PD1)/programmed death-ligand 1 (PD-L1) (70.3%).

Tusamitamab ravtansine is being developed in NSQ NSCLC. The randomized Phase 3 EFC15858 trial is currently ongoing to evaluate the efficacy and the safety of tusamitamab ravtansine versus docetaxel in previously treated metastatic NSQ NSCLC patients with CEACAM5-positive tumors. The combination therapy with tusamitamab ravtansine is also currently being studied in 2 Phase 2 trials in patients with NSQ NSCLC in second or third-line and first-line settings, ACT16525 in combination with ramucirumab in patients with CEACAM5 positive tumors

previously treated with platinum-based chemotherapy and an immune checkpoint inhibitor, and ACT16146 in combination with pembrolizumab in first-line in patients with CEACAM5-positive and PD-L1-positive tumors.

Other tumor types also express CEACAM5 in tumor cells. The efficacy and the safety of tusamitamab ravtansine will be explored in other indications for which the tumor expresses CEACAM5 and which are also known to be sensitive to anti-tubulin agents such as the metastatic breast cancer (mBC) and the pancreatic adenocarcinoma (PAC).

The prevalence of the high expression (defined as ≥2+ in intensity involving at least 50% of the tumor cells) is 10% in all mBC types in which no high expression was identified in the primary tumors, 14% in triple-negative breast cancer (TNBC), and 15% in pancreatic cancer.

Taxanes are very active agents in the treatment of breast cancer and have shown clinical benefit both in the metastatic and (neo) adjuvant setting (4, 5). Nab-paclitaxel in combination with gemcitabine is one of the two recommended combination therapies in first-line treatment for metastatic pancreatic cancer (6, 7).

The aim of this multi-cohort study is to evaluate the safety and efficacy of tusamitamab ravtansine to potentially improve the efficacy with a favorable safety profile in participants with mBC (Cohort A [monotherapy]) and metastatic pancreatic adenocarcinoma (mPAC; Cohort B [monotherapy] and Cohort C [in combination with gemcitabine]) CEACAM5-positive tumors known to be sensitive to taxanes, which leads to a higher hematological toxicity than tusamitamab ravtansine.

Objectives and endpoints

Objectives	Endpoints
Primary	
• For Cohort A, Cohort B, and Cohort C Part 2: To assess the antitumor activity of tusamitamab ravtansine in mBC and tusamitamab ravtansine monotherapy and in combination with gemcitabine in mPAC	• Objective Response Rate (ORR) of tusamitamab ravtansine, defined as the 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
• For Cohort C Part 1: Confirmation of the recommended tusamitamab ravtansine dose when administered in combination with gemcitabine	• Incidence of dose-limiting toxicites (DLTs) in the 28 Day DLT observation period (Cycle 1)
Secondary	
• To assess the safety and tolerability of tusamitamab ravtansine administered as monotherapy and in combination with gemcitabine	• Incidence of participants with treatment-emergent adverse events (TEAEs), serious adverse events (SAEs) and laboratory abnormalities according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0

• To assess other efficacy parameters of tusamitamab ravtansine administered as monotherapy and in combination with gemcitabine	• Progression-free survival (PFS), defined as the time from the date of first tusamitamab ravtansine administration to the date of the first documented disease progression or death due to any cause, whichever comes first • Disease control rate (DCR), defined as the percentage of participants who have achieved confirmed CR, confirmed PR or stable disease as per RECIST v1.1 • Duration of response (DOR), defined as the time from first documented evidence of confirmed CR or confirmed PR until progressive disease determined per RECIST v1.1 or death from any cause, whichever occurs first
• To assess the immunogenicity of tusamitamab ravtansine	• Incidence of participants with antitherapeutic antibodies (ATAs) against tusamitamab ravtansine
• To assess the pharmacokinetics (PK) of tusamitamab ravtansine and gemcitabine when given in combination	• Pharmacokinetic parameters of tusamitamab ravtansine and gemcitabine

Overall design:

This is 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 mBC (Cohort A) and mPAC (Cohort B) with CEACAM5-positive tumors (defined as CEACAM5 immunohistochemistry [IHC] intensity ≥2+ in ≥50% of tumor cells), and also assessing efficacy (antitumor activity), safety, tolerability, PK, and immunogenicity of tusamitamab ravtansine combined with gemcitabine in participants with mPAC (Cohort C) with CEACAM5-positive tumors.

During the prescreening phase, participants' tumor samples will be collected to evaluate CEACAM5 status (central assessment by IHC). During the screening phase, only participants with mBC and mPAC determined to be CEACAM5-positive will go through protocol screening procedures.

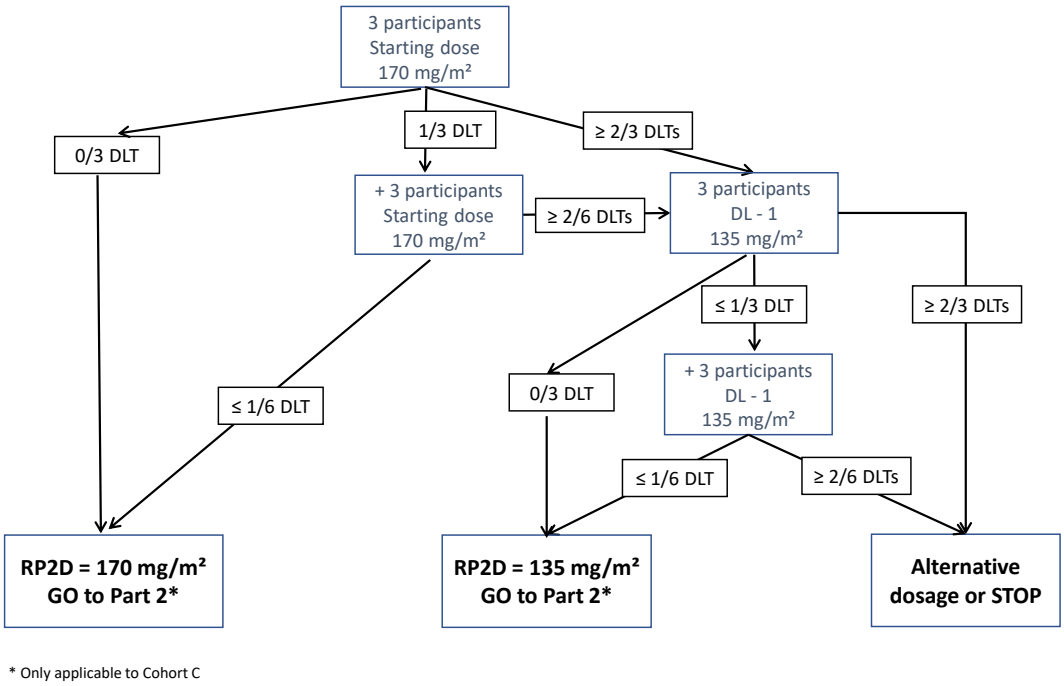
Treatment allocation will be performed using an interactive response technology (IRT). After being screened, the eligible participants will receive tusamitamab ravtansine as single agent treatment or receive tusamitamab ravtansine and gemcitabine combined treatment.

In Cohorts A and B, participants will receive 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 will be 28 days (4 weeks). Cohort C will comprise 2 parts:

Part 1 (Safety Run-In): In Part 1, participants will receive a 170 mg/m² tusamitamab ravtansine loading dose on Day 1, followed by 100 mg/m² every 2 weeks (Q2W); participants will also receive gemcitabine 1000 mg/m^2 on Day 1, Day 8, and Day 15 every 4 weeks (Q4W). In the case that it is decided to reduce the initial loading dose of tusamitamab ravtansine to DL-1 (Figure 1), a tusamitamab ravtansine loading dose of 135 mg/m^2 will be administered to participants on Day 1 of Cycle 1.

Figure 1 - Decision tree for tusamitamab ravtansine loading dose in Cohort C



* Only applicable to Cohort C

The starting dose for tusamitamab ravtansine is selected as the maximum tolerated dose (MTD) used in studies evaluating tusamitamab ravtansine as loading-dose monotherapy. Enough participants will be enrolled in Part 1 to achieve 3 to 12 participants evaluable for DLTs to confirm the recommended dose. The tolerability of the combination is assessed in Part 1 according to the algorithm illustrated in Figure 1. The DLT observation period is the first cycle (approximately 28 days). A DLT-evaluable participant must have completed 1 cycle of treatment or have been discontinued from study treatment because of a DLT; DLT-nonevaluable participants will be replaced. A minimum delay of 1 week is required between the initial dose in the first participant treated in a DL cohort and dosing of the next 2 participants treated at the same DL.

In Part 2 of the study, the recommended dose confirmed in Part 1 will be evaluated for activity in 24 to 27 additional participants. A total of 30 participants, including participants treated at the recommended dose in Part 1, will be evaluated for activity.

Brief summary:

This is a single group, treatment, Phase 2, no masking, 3 arm study to evaluate efficacy (antitumor activity), safety, and immunogenicity of tusamitamab ravtansine in male and female participants aged 18 years or more with mBC (Cohort A [monotherapy]) and mPAC (Cohorts B [monotherapy] and C [in combination with gemcitabine]) with CEACAM5-positive tumors (defined as CEACAM5 IHC intensity ≥2+ in ≥50% of tumor cells).

Number of participants:

Approximately 118 participants will be screened to achieve 94 participants enrolled to study intervention and evaluable. The table below provides the approximate number of participants prescreened, screened, treated and evaluable per study arm:

Table 1 - Approximate number of participants per study arm

Approximate number of participants	mBC	mPAC	
	Cohort A	Cohort B	Cohort C
Prescreened	440	242	90
Screened	44	36	38
Treated and Evaluable	35	29	30

Intervention groups and duration:

- **Prescreening period:** Prescreening Informed Consent will be signed by the participant and participants' tumor samples will be collected to evaluate CEACAM5 status.

The duration of the study for a participant, irrespective of the study cohort, will include:

- **Screening period**: up to 28 days.
- **Treatment period**: once successfully screened, enrolled participants may receive study intervention until documented disease progression, unacceptable toxicity, new anticancer therapy initiation, or the participant's or Investigator's decision to stop the treatment. Each cycle of treatment will last for 2 weeks. After discontinuing study intervention, participants will return to the study site approximately 30 days after the last IMP administration or before the participant receives another anti-cancer therapy, whichever is earlier, for end-of-treatment (EOT) assessments.
- **Safety follow-up visit**: Serious adverse events/adverse events of special interest (AESIs) (regardless of relationship with study treatment) and IMP-related adverse events (AEs) ongoing at the end of study treatment, and any new IMP-related AEs/SAEs/AESIs will be followed until resolution or stabilization. The follow-up visit will be performed 90 days after the last IMP administration. If ongoing IMP-related AEs/SAEs/AESIs are resolved or stabilized, no further safety follow-up visit will be needed, otherwise an on-site follow-up visit will be performed every 12 weeks.

Participants who stop treatment before documented progressive disease (achieving stable disease, or CR or PR) should undergo a tumor assessment and an on-site follow-up visit every 12 weeks until radiological disease progression, the start of new anti-cancer therapy, withdrawal of participant's consent, or cut-off date for secondary efficacy endpoints, whichever comes first. After documented progressive disease or the start of a new anticancer therapy, participants will be followed until any ongoing IMP-related AEs/SAEs/AESIs are resolved or stabilized.

The cut-off date for the interim analysis corresponds to the date when the first 15 treated evaluable participants in Cohort C have had at least 2 postbaseline tumor assessments, experienced confirmed objective response, or have discontinued the study for any reason. For participants with 2 postbaseline tumor assessments and occurrence of response at the second postbaseline tumor assessment, the confirmatory assessment will also be included.

The study cut-off for the primary analysis (ORR) for each cohort corresponds to the date on which all treated evaluable participants of the cohort have had at least 2 postbaseline tumor assessments, experienced confirmed objective response, or have discontinued the study for any reason. For participants with 2 postbaseline tumor assessments and occurrence of response at the second postbaseline tumor assessment, the confirmatory assessment will also be included. The cut-off can be up to approximately 20 weeks after the date of the first IMP administration of the last participant of the cohort: 16 weeks for 2 tumor assessments and at least 4 weeks if a confirmation of response is needed.

The analysis cut-off date for secondary efficacy endpoints including DOR and PFS (final cut-off date) will be 6 months after the cut-off date of the primary analysis. The primary analysis of ORR and DCR will also be updated at that time.

After the cut-off date for the secondary efficacy endpoints, participants with observed clinical benefit who are still receiving study treatment can continue study treatment until progressive disease, unacceptable toxicity, new anticancer therapy initiation, or the participant's or Investigator's decision to stop the treatment, and will continue to undergo all assessments as per the study flow chart.

The expected duration of study intervention for participants may vary, based on progression date and the cohort; median expected duration of study per participant is estimated at 8 months for the mBC cohort and 6 months for the mPAC cohorts (up to 1 month for screening, a median of 4 or 2 months for treatment in the mBC and mPAC cohorts respectively, a median of 1 month for EOT, and follow-up visit 90 days after the last IMP administration).

Study interventions

Study intervention is tusamitamab ravtansine (SAR408701) administered as monotherapy or in combination with gemcitabine.

Investigational medicinal product(s)

Tusamitamab ravtansine

- Formulation: tusamitamab ravtansine (SAR408701) is supplied as a 25 mL extractable volume of concentrate for solution for infusion of 125 mg contained in a 30 mL Type I glass vial.
- Route(s) of administration: intravenous (IV) infusion.
- Dose regimen: For Cohorts A and B, tusamitamab ravtansine (SAR408701) loading dose at 170 mg/m² will be administered via IV infusion over 1 hour 30 minutes on Day 1 of Cycle 1, followed by 100 mg/m² Q2W from Cycle 2 and in all other cycles. For Cohort C, tusamitamab ravtansine (SAR408701) loading dose at 170 mg/m² (or 135 mg/m^2) will be

administered via IV infusion over 1 hour 30 minutes on Day 1 of Cycle 1, followed by 100 mg/m² Q2W. To prevent hypersensitivity reactions, premedication will be given before each administration (see below).

For participants with a body surface area (BSA) >2.20 m², the dose will be calculated based on a BSA of 2.20 m².

Gemcitabine

- Formulation: gemcitabine is supplied as lyophilized powder for reconstitution or as a solution for infusion.
- Route(s) of administration: intravenous (IV) infusion.
- Dose regimen: For Cohort C, gemcitabine at 1000 mg/m² will be administered via IV infusion over 30 minutes on Day 1, Day 8, and Day 15 of each cycle (Q4W). If gemcitabine is administered on the same day as tusamitamab ravtansine, gemcitabine administration will be started after tusamitamab ravtansine infusion.

Noninvestigational medicinal products (NIMP)

Premedication:

- Premedication with Histamine H1 antagonist (oral diphenhydramine 50 mg or equivalent [eg, dexchlorpheniramine] given approximately 15 minutes to 1 hour before tusamitamab ravtansine administration depending on the administration form IV or oral [15 minutes prior for IV and 1 hour prior for oral]) is required for all participants before administration of tusamitamab ravtansine. If a participant has experienced an infusion reaction in a previous tusamitamab ravtansine administration, premedication will also include dexamethasone 10 mg IV for future infusions. In case participant does not experience any hypersensitivity reactions after 4 cycles, the premedication can be discontinued at the discretion of the Investigator.
- Premedication for gemcitabine: Antiemetic preventive therapy must be given according to ASCO guidelines and the local practice. Gemcitabine is known as a low-emetic-risk antineoplastic agent. According to ASCO anti-emetics guidelines updated on May 6th, 2020, adults treated with low-emetic-risk antineoplastic agents should be offered a single dose of a 5-HT3 receptor antagonist or a single 8◦mg dose of dexamethasone before antineoplastic treatment (8).

Posttrial access to study medication:

Interventions should be decided by the Investigator per clinical practice.

Statistical considerations:

- **Sample size calculations:**

  As this study is not intended to explicitly test a hypothesis, calculations of power and Type I error were not considered in the study design. Assuming prescreening failure rates of 90% for mBC Cohort A, 85% for mPAC Cohort B, 58% for mPAC Cohort C, and a screening failure rate of 20% for the 3 cohorts, approximately 440 participants will be

prescreened to achieve up to 35 treated evaluable participants in mBC Cohort A; approximately 242 participants will be prescreened to achieve up to 29 treated evaluable participants in mPAC Cohort B; and approximately 90 participants will be prescreened to achieve up to 30 treated evaluable participants in mPAC Cohort C. These participants will be evaluable for activity (at least 1 postbaseline tumor assessment, early progression, or death due to progressive disease).

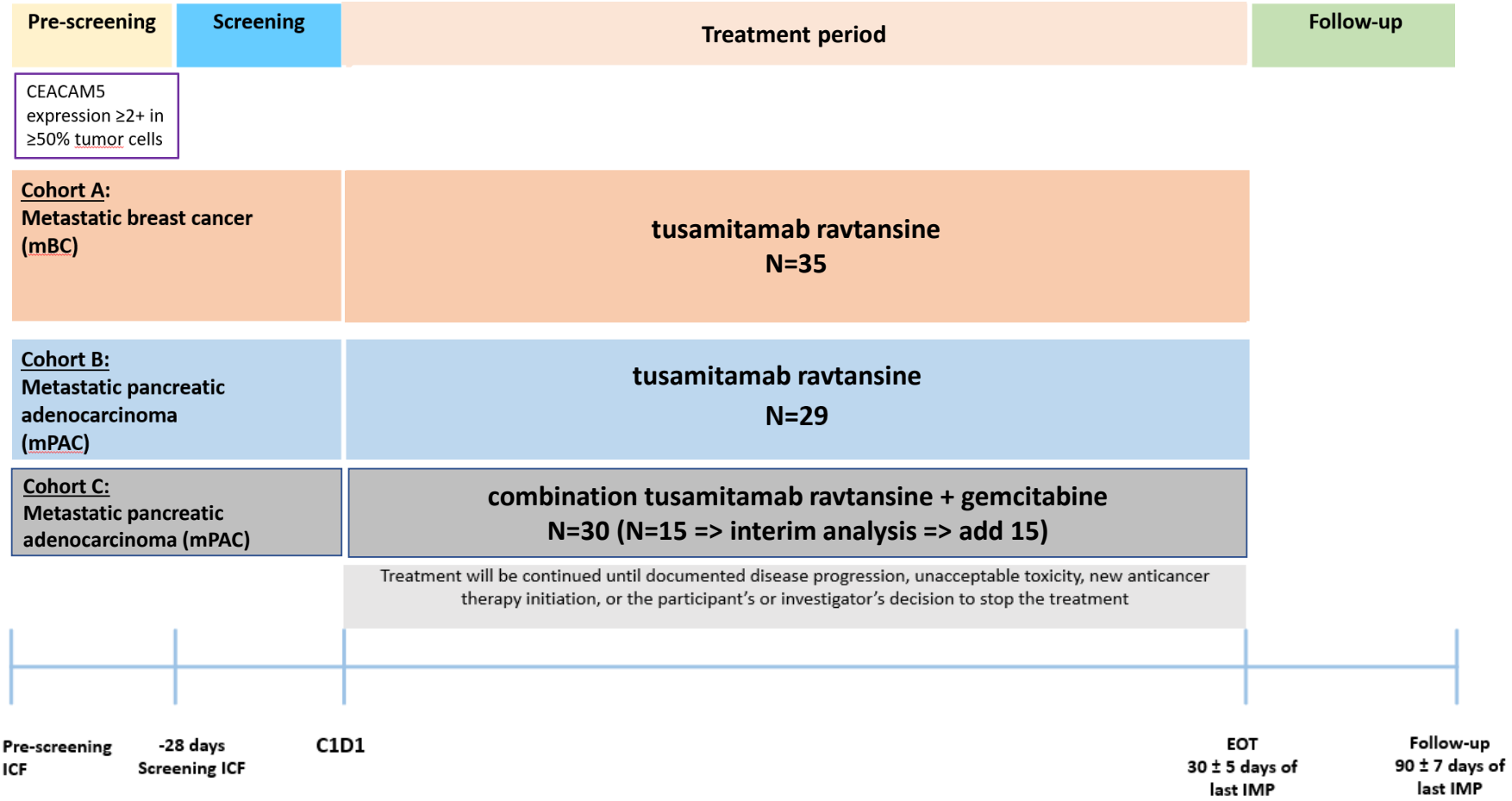
- **Main analysis population:**
  - **All-treated population:** All registered participants exposed to the study treatment, regardless of the amount of treatment administered. This population is the primary population for all efficacy parameters.
  - **Activity population:** All treated participants who have measurable disease at study entry and at least 1 postbaseline evaluable tumor assessment. Participants with no postbaseline evaluable tumor assessment but with an early clinical progression or who died from disease progression will also be included in this set. This population is the secondary population for analysis of efficacy parameters.
  - **ATA population:** All treated participants with at least 1 postbaseline ATA result (negative, positive, or inconclusive).
  - **DLT-Evaluable (Cohort C Part 1):** Participants who received 1 cycle with at least 80% of the intended dose for both tusamitamab ravtansine at each of the first 2 infusions and gemcitabine at each of the 3 first infusions unless they discontinued the study intervention before the end of Cycle 1 due to a DLT.
  - **PK population:** All treated participants with at least 1 postbaseline PK result with adequate documentation of dosing and sampling dates and times.
- **Analysis of primary endpoint:**
  - Objective response rate will be summarized for the All-treated population using descriptive statistics and 95% exact CIs will be provided using the Clopper-Pearson method.
  - Objective response rate will also be summarized on the activity population as a supplementary analysis.
  - For Part 1 of Cohort C, DLTs observed during the 28 day DLT observation period (Cycle 1) will be summarized on the DLT-evaluable population, by dose level.
- **Analysis of secondary efficacy endpoints:**
  - Progression-free survival will be summarized on the All-treated population using Kaplan-Meier methods. The median PFS time and associated 95% CI will be provided along with probabilities of being progression-free at different time points.
  - The DCR will be summarized for the All-treated population with descriptive statistics. In addition, 2-sided 95% CIs will be computed using the Clopper-Pearson method.
  - The DOR will only be summarized on the subgroup of participants who have achieved confirmed objective response in the All-treated population with descriptive statistics using Kaplan-Meier methods. The median DOR and associated 95% CI will be provided.

- **Analysis of safety endpoints:**
  - Number and percentage of participants experiencing TEAEs by primary system organ class (SOC) and preferred term (PT) will be summarized by NCI-CTCAE v5.0 grade (all grades and Grade ≥3) for the All-treated population. Similar summaries will be prepared for treatment-related TEAEs, TEAEs leading to definitive discontinuation, TEAEs leading to dose modification, serious TEAEs, TEAEs with fatal outcome, AESIs, and AEs/SAEs occurring during the post-treatment period. In addition, the number (%) of participants with any Grade 5 AE (TEAE and post-treatment) will be summarized.
  - Hematology and clinical chemistry results will be graded according to the NCI-CTCAE v5.0, when applicable. Number and percentage of participants with laboratory abnormalities (all grades and by grade) using the worst grade during the treatment period will be provided for the All-treated population.

Data Monitoring/Other committee: No

1.2 SCHEMA

Figure 2 - Graphical study design



C = cycle; CEACAM5 = carcinoembryonic antigen-related cell adhesion molecule 5; D = Day; EOT = end-of-treatment; ICF = informed consent form; IMP = investigational medicinal product; mBC = metastatic breast cancer, mPAC = metastatic pancreatic adenocarcinoma, N = number of participants.

1.3 SCHEDULE OF ACTIVITIES (SOA)

1.3.1 Study procedures flowchart for Cohort A and B

Procedure	Prescreening[a]	Screening[b]	Treatment Cycle 1	Treatment Cycle 2 and subsequent (14 ±2 days from previous infusion)		End of treatment	Follow-up[c]	Notes
Day(D)		**(Days prior to initial infusion)**	**D1 Pre-infusion**	**D1 Pre-infusion[d] (±2 days)**	**Every 8 weeks (±7 days)**	**D30 after last infusion (±5 days)**	**D90 after last infusion (±7 days)**	
CEACAM5 expression status (archival or fresh tumor tissue[d]) after prescreening informed consent	X							Assessed by central IHC after prescreening informed consent.
CEACAM5 expression status for mBC on primary tumor (archival, if available)[f]		X						
FFPE sections for RNA and DNA analysis (archival or fresh tumor tissue)[g]		X						
Informed consent		X						
IRT contact	X	X	X	X		X	X	
Inclusion and exclusion criteria		≤28	X					
Demography		≤28						
Medical/surgical/disease history		≤28						Includes histologic types, stage at diagnosis, disease extent at study entry and specific mutations
Physical examination, ECOG performance status		≤7	X	X		X	X	Examination of major body systems including cardiovascular, central nervous system, respiratory system, gastrointestinal system, hepatomegaly, splenomegaly, lymphadenopathy.
Height		≤7						

Procedure	Prescreening[a]	Screening[b]	Treatment Cycle 1	Treatment Cycle 2 and subsequent (14 ±2 days from previous infusion)		End of treatment	Follow-up[c]	Notes
Day(D)		**(Days prior to initial infusion)**	**D1 Pre-infusion**	**D1 Pre-infusion[d] (±2 days)**	**Every 8 weeks (±7 days)**	**D30 after last infusion (±5 days)**	**D90 after last infusion (±7 days)**	
Weight, BSA		≤7	X	X		X		On Day 1 of each treatment cycle, the participant's BSA will be determined using the current weight and baseline height.
Vital signs		≤7	X	X		X		Temperature, blood pressure, and pulse rate
Serum or urine pregnancy test (WOCBP only)[h]		≤7		Every 4 weeks		X		Mandatory serum test at screening and EOT, serum or urine test during study treatment period.
HBV & HCV serology; HIV test (only if required at country level)		X						
Laboratory assessments[i]		≤7	X[j]	X		X		During first 2 cycles, hematology and liver function tests will be assessed weekly.
12-lead ECG		≤7		X		X		
Specific ocular tests		≤28				X		Include assessment of ocular/visual symptoms and ocular exams including visual acuity, slit-lamp under dilatation, and Schirmer's test at screening, EOT and whenever clinically indicated
Assessment of ocular/visual symptoms			X	X				
Tusamitamab ravtansine intervention			X	X				Participants should receive study intervention until documented disease progression, unacceptable toxicity, new anticancer therapy initiation, or the participant's or Investigator's decision to stop the treatment

Procedure	Prescreening[a]	Screening[b]	Treatment Cycle 1	Treatment Cycle 2 and subsequent (14 ±2 days from previous infusion)		End of treatment	Follow-up[c]	Notes
Day(D)		**(Days prior to initial infusion)**	**D1 Pre-infusion**	**D1 Pre-infusion[d] (±2 days)**	**Every 8 weeks (±7 days)**	**D30 after last infusion (±5 days)**	**D90 after last infusion (±7 days)**	
AE assessment	X[k]	←==========				==========→	X[c]	
Concomitant medication review		←==========				==========→		
Tumor assessment - RECIST v1.1 - CT/MRI[l]		≤28			X	X	X	Imaging assessments are to be scheduled using the Cycle 1, Day 1 date as the reference for all time points and are not to be scheduled based on the date of the previous imaging time point.
Circulating CEA	X	≤28			X	X	X	On infusion days, to be performed before infusion or the day before
Whole blood for circulating tumoral cells (CTC)			X					To be performed on Cycle 1 Day 1 before infusion or the day before. Samples will be taken from approximately 5 participants per indication (mBC, mPAC).
Plasma for tumor cfDNA and whole blood for germline DNA			X					To be performed on Day 1 before infusion or the day before
tusamitamab ravtansine immunogenicity (ATA)[m]			X[m]	X[m]		X		On infusion days, to be performed before infusion or the day before

AE = adverse event; AESI = adverse event of special interest; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AP = alkaline phosphatase; AST = aspartate aminotransferase; ATA = anti-therapeutic antibody; BSA = body surface area; BUN = blood urea nitrogen; CEA = carcinoembryonic antigen; CEACAM5 = carcinoembryonic antigen-related cell adhesion molecule 5; cfDNA = circulating free deoxyribonucleic acid; CT = computed tomography; CTC = circulating tumoral cells; CR = complete response; D = Day; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EOT = end-of-treatment; FFPE = formalin-fixed paraffin embedded; HCV = hepatitis C virus; HIV = human immunodeficiency virus; ICF = informed consent form; IHC = immunohistochemistry; IMP = investigational medicinal product; IRT = interactive response technology; LDH = lactate dehydrogenase; mBC = metastatic breast cancer; mPAC = metastatic pancreatic adenocarcinoma; MRI = magnetic resonance imaging; PR = partial response; RECIST = response evaluation criteria in solid tumors; RNA = ribonucleic acid; SAE = serious adverse event; WBC = white blood cell; WOCBP = woman of childbearing potential.

a Prescreening Informed Consent will be signed by the participant before CEACAM5 assay on archival or fresh tumor tissue.

b Informed consent should be signed before any study specific procedures. It can be signed more than 28 days prior to initiation of therapy. Screening time indicates in which timeframe exams used to support eligibility have to be done prior to initiation of therapy. Routine baseline tests performed prior to ICF signature do not need to be repeated as long as they are within the screening-defined timeframe. Assessments must be performed prior to first IMP administration: participants must have confirmed CEACAM5 expression as assessed centrally. Baseline evaluation should be completed within 1 week prior to initiation of therapy, except for tumor assessment, circulating CEA, and ocular tests that may be performed within 4 weeks prior to the first IMP administration. Results of these tests should be reviewed by the Investigator prior to initiation of therapy.

c At the follow-up visit, SAEs/AESIs (regardless of relationship with study treatment) and IMP-related AEs ongoing at the end of study treatment, and any new IMP-related AEs/SAEs/AESIs will be followed until resolution or stabilization (stabilization is defined as an event ongoing without any change for at least 3 months). Further anti-cancer treatment will be collected at the follow-up visit, including date of progression if any. Participants who stopped treatment before documented progressive disease (achieving stable disease, or CR or PR) should undergo a tumor assessment and an on-site follow-up visit every 12 weeks until radiological disease progression, the start of new anti-cancer therapy, withdrawal of participant's consent, or cut-off date for secondary efficacy endpoints, whichever comes first. After documented progressive disease or the start of a new anti-cancer therapy, participants will be followed until any ongoing IMP-related AEs/SAEs/AESIs are resolved or stabilized. Participants with documented disease progression should attend an on-site follow-up visit 90 days after the last IMP administration. If ongoing IMP-related AEs/SAEs/AESIs are resolved or stabilized, no further safety follow-up visit is needed. If IMP-related AEs/SAEs/AESIs ongoing, an on-site follow-up visit will be performed every 12 weeks.

d D1 of Cycle 2 and of each subsequent cycle corresponds to D15 of the previous cycle (±2 days). As of Cycle 2, procedures can be done on the day of infusion (before infusion) or the day before.

e mBC: At the metastatic site (mandatory); mPAC: Preferably at the metastatic site; Cell collections (eg, from pleural effusion) processed as FFPE blocks are acceptable.

f If available, 3 x 5 µm slides from the surgery material at the breast cancer diagnosis (primary tumor or local lymph nodes) are requested for CEACAM5 assessment.

g At least 3 x 10 µm slides (best) or 6 x 5 µm slides (or equivalent to the same total amount of material) from FFPE tissue (from same sample as the one used for CEACAM5 expression status if possible) from treatment start for both mBC and mPAC (only screened participants).

h Women of childbearing potential (WOCBP) must have a negative serum pregnancy test result within 7 days prior to the initial dose of IMP. A pregnancy test (urine or serum as required by local regulations) will be repeated every 4 weeks before each IMP administration and at the EOT evaluation (30 ±5 days after the last IMP administration).

i Hematology: hemoglobin, hematocrit, RBC, WBC with differential, platelet counts (If Grade 4 neutropenia, assess ANC every 2 to 3 days until ANC ≥0.5 x 10^9/L). Liver function tests: AST, ALT, total bilirubin, conjugated bilirubin, AP. Renal function tests: urea (or BUN) and creatinine. Electrolytes: sodium, potassium, calcium, phosphate, chloride. Others: glucose, LDH, albumin and total proteins. In case of Grade ≥3 liver function abnormal tests, additional tests will be repeated every 2-3 days until recovery to baseline value. Additional tests will be performed when clinically appropriate. Tests can be performed on the same day or within the 2 days before initiating study intervention.

j Day 1 hematology, blood chemistry and coagulation tests may be omitted if baseline test performed within 7 days are normal. If baseline tests are abnormal, they should be repeated within 2 days of first study intervention.

k Only AEs related to the fresh biopsy procedure (if applicable) and occurring within 1 month after the fresh biopsy will be recorded in the eCRF.

l Chest, abdomen, pelvic CT-scan or MRI and any other examinations as clinically indicated will be performed to assess disease status at baseline and then every 8 weeks (±7 days) until EOT, and then every 12 weeks until progressive disease, new anticancer therapy, death, withdrawal of participant's consent, or study cut-off date for secondary efficacy endpoints, whichever comes first. Bone CT-scan or MRI and other examinations should be performed if clinically indicated. Brain CT scan or MRI should be performed at baseline and followed during treatment only for participants with brain lesions at baseline.

m Tusamitamab ravtansine ATA samples will be collected before start of infusion of each cycle until C3, at C7, and thereafter every 6 cycles (ie, C13, C19, etc). The remaining plasma volume may also be used for further investigations including pharmacokinetics if deemed relevant in case of ATA positive results.

1.3.2 Study procedures flowchart for Cohort C

Procedure	Prescreening[a]	Screening[b]	Treatment Cycle 1 and subsequent (28±3 days from previous infusion)				End of treatment	Follow-up[c]	Notes
Day(D)		**(Days prior to initial infusion)**	**D1 Pre-infusion[d]**	**D8 Pre-infusion (±1 day)**	**D15 Pre-infusion (±2 days)**	**Every 8 weeks (±7 days)**	**30 days after last infusion (±5 days)**	**90 days after last infusion (±7 days)**	
CEACAM5 expression status (archival or fresh tumor tissue[e]	X								Assessed by central IHC after prescreening informed consent.
FFPE sections for RNA and DNA analysis (archival or fresh tumor tissue)[f]		X	X (if not obtained during screening)						If not done during Screening, to be performed on Cycle 1 Day 1 before infusion
Informed consent		X							
IRT contact	X	X	X		X		X	X	
Inclusion and exclusion criteria		≤28	X						Only to be performed on Cycle 1 Day 1
Demography		≤28							
Medical/surgical/ disease history		≤28							Includes histologic types, stage at diagnosis, disease extent at study entry and specific mutations
Physical examination, ECOG performance status		≤7	X	X	X		X	X	Examination of major body systems including cardiovascular, central nervous system, respiratory system, gastrointestinal system, hepatomegaly, splenomegaly, lymphadenopathy.
Height		≤7							
Weight, BSA		≤7	X	X	X		X		On each treatment cycle, the participant's BSA will be determined using the current weight and baseline height.
Vital signs		≤7	X	X	X		X		Temperature, blood pressure, and pulse rate
Serum or urine pregnancy test (WOCBP only)[h]		≤7	X				X		Mandatory serum test at Screening and EOT; serum or urine test during study treatment period.
HBV & HCV serology; (HIV test if required at country level)		X							

Procedure	Prescreening[a]	Screening[b]	Treatment Cycle 1 and subsequent (28±3 days from previous infusion)				End of treatment	Follow-up[c]	Notes
Day(D)		**(Days prior to initial infusion)**	**D1 Pre-infusion[d]**	**D8 Pre-infusion (±1 day)**	**D15 Pre-infusion (±2 days)**	**Every 8 weeks (±7 days)**	**30 days after last infusion (±5 days)**	**90 days after last infusion (±7 days)**	
Laboratory assessments[i]		≤7	X[i]	X	X		X		
12-lead ECG		≤7	X		X		X		D1 ECG performed only from Cycle 2
Specific ocular tests		≤28					X		Include assessment of ocular/visual symptoms and ocular exams including visual acuity, slit-lamp under dilatation, and Schirmer's test at screening, EOT, and whenever clinically indicated
Assessment of ocular/visual symptoms			X		X				
Tusamitamab ravtansine intervention			X		X				Participants should receive study intervention until documented disease progression, unacceptable toxicity, new anticancer therapy initiation, or the participant's or Investigator's decision to stop the treatment
Gemcitabine intervention			X	X	X				
AE assessment	X[i]	←==========					==========→	X[c]	
Concomitant medication review		←==========					==========→		
Tumor assessment - RECIST v1.1 - CT/MRI[k]		≤28				X	X	X	Imaging assessments are to be scheduled using the Cycle 1, Day 1 date as the reference for all time points, and are not to be scheduled based on the date of the previous imaging time point.
Circulating CEA	X	≤28				X	X	X	To be performed pre-infusion or the day before, and at EOT visit
Plasma for tumor cfDNA and whole blood for germline DNA			X						To be performed only pre-infusion on Cycle 1 Day 1 or the day before
Immunoglobulin G			X						To be performed only pre-infusion on Cycle 1 Day 1 or the day before
Tusamitamab ravtansine PK and gemcitabine PK ; immunogenicity (ATA);			←==========						Refer to PK/ATA flowcharts in Section 1.3.3; see also Section 8.4; Section 8.7

AE = adverse event; AESI = adverse event of special interest; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AP = alkaline phosphatase; AST = aspartate aminotransferase; ATA = antitherapeutic antibody; BSA = body surface area; BUN = blood urea nitrogen; CEA = carcinoembryonic antigen; CEACAM5 = carcinoembryonic antigen-related cell adhesion molecule 5; cfDNA = circulating free deoxyribonucleic acid; CT = computed tomography; CTC = circulating tumoral cells; CR = complete response; D = Day; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EOT = end-of-treatment; FFPE = formalin-fixed paraffin embedded; HCV = hepatitis C virus; HIV = human immunodeficiency virus; ICF = informed consent form; IHC = immunohistochemistry; IMP = investigational medicinal product; IRT = interactive response technology; LDH = lactate dehydrogenase; mBC = metastatic breast cancer; mPAC = metastatic pancreatic adenocarcinoma; MRI = magnetic resonance imaging; PK = pharmacokinetics; PR = partial response; RECIST = response evaluation criteria in solid tumors; RNA = ribonucleic acid; SAE = serious adverse event; WBC = white blood cell; WOCBP = woman of childbearing potential.

a Prescreening Informed Consent will be signed by the participant before CEACAM5 assay on archival or fresh tumor tissue.

b Informed consent should be signed before any study specific procedures. It can be signed more than 28 days prior to initiation of therapy. Screening time indicates in which timeframe exams used to support eligibility have to be done prior to initiation of therapy. Routine baseline tests performed prior to ICF signature do not need to be repeated as long as they are within the screening-defined timeframe. Assessments must be performed prior to first IMP administration: participants must have confirmed CEACAM5 expression as assessed centrally. Baseline evaluation should be completed within 1 week prior to initiation of therapy, except for tumor assessment, circulating CEA, and ocular tests that may be performed within 4 weeks prior to the first IMP administration. Results of these tests should be reviewed by the Investigator prior to initiation of therapy.

c At the follow-up visit, SAEs/AESIs (regardless of relationship with study treatment) and IMP-related AEs ongoing at the end of study treatment, and any new IMP-related AEs/SAEs/AESIs will be followed until resolution or stabilization (stabilization is defined as an event ongoing without any change for at least 3 months). Further anticancer treatment will be collected at the follow-up visit, including date of progression, if any. Participants who stopped treatment before documented progressive disease (achieving stable disease, or CR or PR) should undergo a tumor assessment and an on-site follow-up visit every 12 weeks until radiological disease progression, the start of new anticancer therapy, withdrawal of participant's consent, or cut-off date for secondary efficacy endpoints, whichever comes first. After documented progressive disease or the start of a new anticancer therapy, participants will be followed until any ongoing IMP-related AEs/SAEs/AESIs are resolved or stabilized. Participants with documented disease progression should attend an on-site follow-up visit 90 days after the last IMP administration. If ongoing IMP-related AEs/SAEs/AESIs are resolved or stabilized, no further safety follow-up visit is needed. If IMP-related AEs/SAEs/AESIs ongoing, an on-site follow-up visit will be performed every 12 weeks.

d D1 of Cycle 2 and of each subsequent cycle corresponds to D29 of the previous cycle (±3 days). As of Cycle 2, procedures can be done on the day of infusion (before infusion) or the day before.

e mPAC: Preferably at the metastatic site; cell collections (eg, from pleural effusion) processed as FFPE blocks are acceptable.

f At least 3 × 10 µm slides (best) or 6 × 5 µm slides (or equivalent to the same total amount of material) from FFPE tissue (from same sample as that used for CEACAM5 expression status, if possible) from treatment start for mPAC (only screened participants).

g Women of childbearing potential (WOCBP) must have a negative serum pregnancy test result within 7 days prior to the initial dose of IMP. A pregnancy test (urine or serum as required by local regulations) will be repeated every 4 weeks before each IMP administration and at the EOT evaluation (30±5 days after the last IMP administration).

h Hematology: hemoglobin, hematocrit, RBC, WBC with differential, platelet counts (If Grade 4 neutropenia, assess ANC every 2 to 3 days until ANC ≥0.5 × 10^9/L). Liver function tests: AST, ALT, total bilirubin, conjugated bilirubin, AP. Renal function tests: urea (or BUN) and creatinine. Electrolytes: sodium, potassium, calcium, phosphate, chloride. Others: glucose, LDH, albumin and total proteins. In case of Grade ≥3 liver function abnormal tests, additional tests will be repeated every 2-3 days until recovery to baseline value. Additional tests will be performed when clinically appropriate. Tests can be performed on the same day or within the 2 days before initiating study intervention.

i Day 1 hematology, blood chemistry and coagulation tests may be omitted if baseline test performed within 7 days are normal. If baseline tests are abnormal, they should be repeated within 2 days of first study intervention.

j Only AEs related to the fresh biopsy procedure (if applicable) and occurring within 1 month after the fresh biopsy will be recorded in the eCRF.

k Chest, abdomen, pelvic CT scan or MRI and any other examinations as clinically indicated will be performed to assess disease status at baseline and then every 8 weeks (±7 days) until EOT, and then every 12 weeks until progressive disease, new anticancer therapy, death, withdrawal of participant's consent, or study cut-off date for secondary efficacy endpoints, whichever comes first. Bone CT scan or MRI and other examinations should be performed if clinically indicated. Brain CT scan or MRI should be performed at baseline and followed during treatment only for participants with brain lesions at baseline.

1.3.3 PK/ATA flow charts for tusamitamab ravtansine and gemcitabine samples for Cohort C

1.3.3.1 First 10 participants

1.3.3.1.1 Cycle 1

	Intervention period	C1												
	Day	**D1**						**D4**	**D8**					**D15**
tusamitamab ravtansine	**IV infusion**	X----------	---------X											X
	Sample RNT (hours) Ref. tusamitamab SOI	SOI	EOI	EOI +3 h				72 h	168 h					336 h (SOI)
	Sample time window	(-24 h, SOI)	±10 min	±30 min				±5 h	±24 h					±48 h
	PK sample ID (SAR408701)	P00[a]	P01	P02				P03	P04					P05[a,b]
	ATA sample ID	AB00[a]												AB01[a, b]
gemcitabine	**IV infusion**	X----------	----------X						X----------	----------X				
	Sample RNT (hours) Ref. gemcitabine SOI	**SOI**	**EOI**	**EOI +15 min**	**1 h**	**1 h 30 min**	**2 h**		**SOI**	**EOI**	**EOI + 15 min**	**1h**	**1 h 30 min**	**2 h**
	Sample time window	(-24h, SOI)	within 5 min of EOI	±5 min	±10 min	±10 min	±20 min		(-24 h, SOI)	within 5 min of EOI	±5 min	±10 min	±10 min	±20 min
	PK sample ID (gemcitabine, dFdU)	PG00[a]	PG01	PG02	PG03	PG04	PG05		PG06[a]	PG07	PG08	PG09	PG10	PG11

Abbreviations: ATA = antitherapeutic antibody; C = cycle; D = day; dFdU=metabolite of gemcitabine; EOI = End of infusion time (ie, for tusamitamab ravtansine: when the pump beeps before flush = 1.5 hour, for gemcitabine = 30 min); EOT = End-of-treatment; h = hour ; IMP = investigational medicinal product; IV = intravenous; min = minutes ; PK = pharmacokinetics; RNT = relative nominal time; SOI = start of infusion.

a Samples collected strictly before start of infusion (SOI), when applicable, tusamitamab ravtansine and gemcitabine predose samples can be collected at the same time before tusamitamab ravtansine administration.

b Sample must be collected even if the infusion planned is not done or delayed on C1D15 and on C2D29 (corresponding to C3D1).

Note: Sampling for PK and ATA may be reduced or stopped during the course of the study upon notification from the Sponsor.

1.3.3.1.2 Cycles 2 through 4, Cycle 7, and End of Treatment visit

Intervention period		C2							C3	C4	C7	EOT
Day		D1	D15			D18	D22	D29	D15	D1	D1	30±5 days after last IMP
tusamitamab ravtansine	**IV infusion**	X	X--	---X				X	X	X	X	
	Sample RNT (hours) Ref. tusamitamab SOI	SOI	SOI	EOI	EOI+3 h	72 h	168 h	336 h (SOI)	SOI	SOI	SOI	
	Sample time window	(-24 h, SOI)	(-24 h, SOI)	±10 min	±30 min	±5 h	±24 h	±48 h	(-24 h, SOI)	(-24 h, SOI)	(-24 h, SOI)	
	PK sample ID (SAR408701)	P00[a]	P01[a]	P02	P03	P04	P05	P06[a,b]	P07[a]	P00[a]	P00[a]	
	ATA sample ID	AB00[a]								AB00[a]	AB00[a,c]	ABF00

Abbreviations: ATA = antitherapeutic antibody; C = cycle; D = day; EOI = End of infusion time (ie, for tusamitamab ravtansine: when the pump beeps before flush = 1.5 hour, for gemcitabine = 30 min); EOT = End-of-treatment; h = hour ; IMP = investigational medicinal product; IV = intravenous; min = minutes ; PK = pharmacokinetics; RNT = relative nominal time; SOI = start of infusion.

a Samples collected strictly before start of infusion (SOI), when applicable, tusamitamab ravtansine and gemcitabine predose samples can be collected at the same time before tusamitamab ravtansine administration.

b Sample must be collected even if the infusion planned is not done or delayed on C1D15 and on C2D29 (corresponding to C3D1).

c tusamitamab ravtansine ATA samples will be collected at SOI at Cycle 7 and thereafter every 3 cycles (ie, C10, C13, 16…)

Note: Sampling for PK and ATA may be reduced or stopped during the course of the study upon notification from the Sponsor.

1.3.3.2 Participants enrolled after the first 10

	Cycle	C1			C2			C3		C4	C7	EOT
	Day	**D1**		**D15**	**D1**		**D15**	**D1**	**D15**	**D1**	**D1**	**30±5 days after last IMP**
tusamitamab ravtansine	**IV infusion**	X----	---X	**X**	X		X	X	X	X	X	
	Sample RNT (hours) Ref. SAR408701 SOI	**SOI**	**EOI**	**SOI**	**SOI**	**EOI+1h**	**SOI**	**SOI**	**SOI**	**SOI**	**SOI**	
	Sample time window	(-24 h, SOI)	±10 min	(-24 h, SOI)	(-24 h, SOI)	±10 min	(-24h, SOI)	(-24 h, SOI)	(-24h, SOI)	(-24 h, SOI)	(-24 h, SOI)	
	PK sample ID (SAR408701)	P00[a]	P01	P02[a]	P00[a]	P01	P02[a]	P00[a]	P01[a]	P00[a]	P00[a]	
	ATA sample ID	AB00[a]		AB01[a]	AB00[a]					AB00	AB00[a,b]	ABF00

Abbreviations: ATA = antitherapeutic antibody; C = cycle; D = day; EOI = end of infusion time (ie, for tusamitamab: when the pump beeps before flush = 1.5 hour); EOT = End-of-treatment visit; IMP = investigational medicinal product; IV = intravenous; PK = pharmacokinetics; RNT = relative nominal; SOI = start of infusion.

a Samples collected strictly before start of infusion (SOI)

b tusamitamab ravtansine ATA samples will be collected at SOI at Cycle 7 and thereafter every 3 cycles (ie, C10, C13, 16…)

Note: Sampling for PK and ATA may be reduced or stopped during the course of the study upon notification from the Sponsor.

2 INTRODUCTION

The CEACAM5 is one of the 7 members of the CEACAM subgroup of a family of glycoproteins involved in cell adhesion (1). It was first described in 1965 as a tumor-associated antigen in human colon cancer tissue extracts (2). High levels of CEACAM5 expression have since been observed in several epithelial tumors, while in normal adults, its expression is limited to only a few tissues (1, 3). Immunostaining of CEACAM5 in a large panel of human tumor tissue microarray samples has shown the highest prevalence of cell surface CEACAM5 expression in adenocarcinoma of the colon and the stomach, and in its subtype signet ring cells as well as in NSQ NSCLC.

Tusamitamab ravtansine is an ADC combining hu769_4D4, a humanized antibody that recognizes selectively the A3-B3 extracellular domain of CEACAM5, with the potent cytotoxic maytansinoid derivative DM4, which inhibits microtubule assembly. Tusamitamab ravtansine is expected to selectively deliver DM4 to cancer cells expressing the CEACAM5 antigen.

In the completed main escalation phase of the first-in-human Study TED13751, 31 participants have been treated with tusamitamab ravtansine across 8 dose levels ranging from 5 to 150 mg/m². Treatment-emergent adverse events were seen in 29 of 31 participants in the main dose-escalation phase. Grade ≥3 TEAEs related to tusamitamab ravtansine were seen in 7 participants (22.6%) and were reported as SAEs in 2 participants (6.5%).

The most frequent (in ≥4 of 31 participants [≥12.9%]) all-cause TEAE PTs were asthenia, nausea, and decreased appetite (8 participants [25.8%] each); keratopathy (8 participants [25.8%] any grade; 6 participants [19.4%] Grade ≥3); diarrhea and constipation (7 participants [22.6%] each); diarrhea/colitis combined (9 participants [29%]); fatigue (6 participants [19.4%]); abdominal pain (5 participants [16.1%]); dry eye and xerophthalmia combined (7 participants [22.6%]); and blurred vision and cough (4 participants [12.9%] each). Nervous system disorders occurred in 8 participants; these included paresthesia in 4 participants (12.9%) and peripheral sensory neuropathy in 2 participants (6.5%). Infectious conditions, which included 3 Grade ≥3 events, were observed in 5 participants (16.1%). Except for keratopathy, these events were predominantly of low severity (Grade 1/Grade 2).

The main clinically relevant laboratory abnormality was thrombocytopenia (51.6% [versus 9.7% at baseline]). Neutropenia has been observed in 5 participants (16.1%); 3 had Grade >3 events. Events possibly linked to allergic processes were documented in 2 participants (1 patient with Grade 2 infusion reaction, and 1 patient with Grade 1 eczematous lesions).

During the assessment of preliminary safety data, extracted from the ongoing expansion cohorts, among 114 participants treated at 100 mg/m² tusamitamab ravtansine and treated with right-eye prophylaxis in the expansion phase, TEAEs of the cornea were reported in 31 participants; 29 participants had clear laterality assessments. Preliminary results showed that approximately 93% of corneal events (27 of 29 events) were bilateral, and thus were not impacted by prophylactic treatment. Based on this preliminary result, it was decided to discontinue primary

ocular prophylaxis, and instead consider secondary prophylaxis on a case-by-case basis following an ophthalmologist's recommendation based on assessment of an individual patient.

As of 17 June 2020, 28 patients were treated in the escalation bis loading dose cohort. Median age was 59.5 years (range: 36 to 73 years) and 19 (67.9%) were male. Sixteen patients (57.1%) had Eastern Cooperative Oncology Group (ECOG) performance status was as 1 at the time of study entry. Three patients were treated at the intended dose level 120 mg/m^2, 4 patients at dose level 135 mg/m^2, 8 patients at dose level 150 mg/m^2, and 13 patients at dose level 170 mg/m^2. No dose-limiting toxicity (DLT) was observed at the 120, 135, and 150 mg/m^2 doses. Among the 9 patients evaluable for DLT, 2 patients presented with DLT at the 170 mg/m^2 dose: 1 patient presented with a Grade 2 event of keratitis during Cycle 2 that led to drug withdrawn and the event was resolved after 31 days; 1 patient presented with Grade 2 event of keratopathy during Cycle 2, that was resolved after 33 days and leading to cycle delay and dose reduction. The maximum tolerated dose (MTD) was identified to be 170 mg/m^2 at Cycle 1 followed by 100 mg/m^2 from Cycle 2.

Treatment-emergent adverse events have been reported in 28 patients (100%) with 19 (67.9%) TEAEs were treatment related. The most frequent all-grade TEAEs excluding laboratory AEs (≥3 patients; ≥10%), regardless of relationship to study medication were corneal events including keratopathy and keratitis (10 patients, 35.7%), nausea (6 patients; 21.4%), peripheral neuropathy (6 patients, 21.4%), asthenia (6 patients; 21.4%), abdominal pain (5 patients; 17.9%), dry eye (4 patients; 14.3%), dyspnoea (4 patients; 14.3%), diarrhoea (4 patients; 14.3%), decreased appetite (3 patients; 10.7%), cough (3 patients; 10.7%), and fatigue (3 patients; 10.7%). Among 13 patients treated at the dose of 170 mg/m^2 at Cycle 1, 8 patients had all grades corneal events and 3 patients had Grade 3 corneal event, 3 patients had all grades peripheral neuropathy and none of the patient experienced Grade 3 and 4 or treatment discontinuation due to neuropathy.

The main laboratory abnormalities were Grade 3 anemia (1 patient, 3.7%), thrombocytopenia (1 patient, 3.7%), aspartate aminotransferase (AST)/alanine aminotransferase (ALT) increase (1 patient, 3.7%), and AST increase (1 patient, 3.7%). No neutropenia and Grade 3 or 4 renal abnormalities were reported.

Pooled analyses were performed for the 160 patients treated at 100 mg/m² Q2W.
Treatment-emergent adverse events have been reported in 157 out of 160 treated patients (98.1%): the most frequent all-grade TEAEs (≥16 patients; ≥10% PT) excluding laboratory based AE regardless of relatedness to study medication were asthenia (35.6%), corneal events (31.9%), peripheral neuropathies (26.9%), decreased appetite (22.5%), diarrhea (21.3%), dyspnea (18.8%), nausea (16.9%), constipation (14.4%), abdominal pain (12.5%), cough (11.9%) and vomiting, fatigue (10% each). Among the patients who experienced corneal side effect, 32 patients had an event that led to dose modification (dose delay [24.4%]), and 1 event led to permanent treatment discontinuation. The median duration until recovery of the observed corneal events was 19 days (range: 8 to 264 days). The first occurrence of corneal event was within the first 4 cycles of treatment for 41 patients (80.4% of patients with corneal event).

Based on laboratory data, the Grade 3 to Grade 4 hematological abnormalities included anemia in 8 patients (5.1%), platelets count decrease in 4 patients (2.5%), and no patient with neutropenia. Grade 3 to Grade 4 liver enzymes elevation (AST/ALT) was observed in 9 patients (5.7%) and no "Hy's law" cases have been observed in this cohort.

The safety and PK of tusamitamab ravtansine administered IV Q2W as monotherapy is being further evaluated in Japanese patients with advanced malignant solid tumors in a Phase 1/1b study (TCD15054). As of 17 June 2020, 9 patients have been treated in the main dose-escalation phase (3 patients at the dose level of 80 mg/m² and 6 patients at the dose level of 100 mg/m²) and 8 patients in the ongoing loading dose-escalation cohort. In the main escalation phase, TEAEs have been reported in 8 patients (88.9%) and 2 (22.2%) of them were reported as Grade ≥3 events. Treatment-emergent AEs related to tusamitamab ravtansine were reported in 6 patients (66.7%); only 1 patient (11.1%) had a Grade ≥3 treatment-related event (gastrointestinal hemorrhage). One patient permanently discontinued study treatment due to an AE (Grade 1 blurred vision event).

2.1 STUDY RATIONALE

In the first-in-human study TED13751, a cohort of heavily pretreated NSQ NSCLC patients with CEACAM5-positive tumor at the membrane (≥2+ in intensity involving at least 50% of the tumor cell population) has been treated with tusamitamab ravtansine at the recommended dose of 100 mg/m² every 2 weeks. In the 64 treated patients, tusamitamab ravtansine showed encouraging anti-tumor activity and was associated with a response rate of 20.3% (95% CI: 12.27% to 31.71%); 28 participants (43.8%) had stable disease. Patients were heavily pretreated with a median of 3 prior treatments (1 to 10 lines) for advanced disease, including anti-tubulin agents (60.9%) and anti-PD1/PD-L1 (70.3%).

Tusamitamab ravtansine is being developed in NSQ NSCLC. The randomized Phase 3 EFC15858 trial is currently ongoing to evaluate the efficacy and the safety of tusamitamab ravtansine versus docetaxel in previously treated metastatic NSQ NSCLC patients with CEACAM5-positive tumors. The use of combination therapy with tusamitamab ravtansine is also currently being studied in 2 Phase 2 trials in patients with NSQ NSCLC in second or third-line and first-line settings: tusamitamab ravtansine in combination with ramucirumab in patients with CEACAM5-positive tumors previously treated with platinum-based chemotherapy and an immune checkpoint inhibitor (Study ACT16525), and tusamitamab ravtansine in combination with pembrolizumab as first-line treatment in patients with CEACAM5-positive and PD-L1-positive tumors (Study ACT16146).

Other tumor types also express CEACAM5 in tumor cells. The efficacy and the safety of tusamitamab ravtansine will be explored in other indications such as mBC and PAC, for which the tumor expresses CEACAM5, and which are also known to be sensitive to antitubulin agents.

The prevalence of high CEACAM expression (defined as ≥2+ in intensity involving at least 50% of the tumor cells) is 10% in all mBC types in which no high expression was identified in the primary tumors, 14% in TNBC, and 15% in pancreatic cancer.

Taxanes are very active agents in the treatment of breast cancer and have shown clinical benefit both in the metastatic and (neo) adjuvant settings (4, 5). Nab-paclitaxel in combination with gemcitabine is 1 of the 2 recommended combination therapies in first-line treatment for metastatic pancreatic cancer (6, 7).

The aim of this multi-cohort study is to evaluate the safety and efficacy of tusamitamab ravtansine single agent to potentially improve the efficacy with a favorable safety profile in patients with mBC and mPAC CEACAM5-positive tumors known as sensitive to taxanes, which are associated to a higher hematological toxicity than tusamitamab ravtansine.

Cohort C has been added to evaluate tusamitamab ravtansine (containing the cytotoxic antitubulin agent DM4) in combination with gemcitabine in participants with pancreatic cancer. The preliminary results of mPAC monotherapy cohort in this study showed the prevalence of CEACAM5 high expression was 42%, so the combination of tusamitamab ravtansine and gemcitabine in 2L taxane naïve population may add a new treatment option in pancreatic adenocarcinoma, an indication with a high unmet medical need. When participants with mPAC were treated with tusamitamab ravtansine monotherapy, DCR was about 29% and long treatment duration (4 to 7.5 months) was observed in 8 of 26 patients.

Gemcitabine is approved as first-line treatment for patients with locally advanced or metastatic pancreatic adenocarcinoma. According to National Comprehensive Cancer Network guidelines, gemcitabine in combination with nab-paclitaxel remains the preferred option for subsequent therapy following fluoropyrimidine-based therapy for mPAC. Substituting tusamitamab ravtansine for nab-paclitaxel in a combination regimen with gemcitabine may improve efficacy and offer a better safety profile, particularly with regard to hematological toxicity, as compared to the combination of gemcitabine and nab-paclitaxel.

2.2 BACKGROUND

Metastatic breast cancer:

Breast cancer remains the most common cancer type in women, with 271,270 new cases and 42 750 deaths in the United States (US) in 2019 (9). Overall survival for women with mBC has improved over recent decades. Long-term survival, however, remains poor (10, 11), highlighting the unmet need for a therapy that is effective, improves quality of life (QoL), and prolongs survival.

Anthracycline- or taxane-based regimens are commonly used in the treatment of breast cancer, often in the (neo) adjuvant and first-line metastatic settings (12). Hormonal therapy and human epidermal growth factor receptor 2 (HER2) targeted therapy in combination with chemotherapy are also standard of care depending on the tumor type. However, treatment decisions in subsequent lines are increasingly difficult (13). There is no single accepted standard of care after failure of anthracycline and taxane therapy (14).

Triple-negative breast cancer accounts for 12% to 20% of all breast cancers diagnosed in the US (15, 16). Compared to patients with hormone receptor (HR)-positive or HER2-positive tumors where average survival exceeds 50 months, survival for women with metastatic TNBC (mTNBC) is considerably shorter, ranging from 11 to 17.8 months (17, 18). Triple-negative breast cancer carries a poor prognosis. Chemotherapy is the standard of care. More importantly, there is no clear standard of care in the second-line setting. Response rates are low (approximately 14% for single-agent chemotherapy) and, although they improve with combination therapies, no treatment

regimen has demonstrated definitive improvement in outcomes (19). Recent data demonstrate that immunotherapy and ADC can improve outcomes. Sacituzumab govitecan, which is an ADC, has shown promising anti-cancer activity in patients with mTNBC previously treated with at least two prior lines of systemic therapy based on a single-arm Phase 1/2 clinical trial (20, 21). The confirmatory Phase 3 ASCENT study exploring sacituzumab govitecan in patients with mTNBC has been stopped due to "compelling evidence of efficacy" and the United States Food and Drug Administration (FDA) granted accelerated approval. Nevertheless, survival remains poor. There remains an unmet medical need for TNBC after first-line chemotherapy treatment (19).

Pancreatic adenocarcinoma:

Pancreatic adenocarcinoma is an aggressive gastrointestinal cancer with an estimated annual incidence of over 45 000 cases and an expected death toll of over 38 000 deaths in 2013 in the US, making it the fourth leading cause of cancer death for both men and women. Five-year survival rate is around 6% (22).

Pancreatic adenocarcinoma is characterized by extensive local growth and early metastasis, making surgical control of disease uncommon. As a result, chemotherapeutic agents are often employed in an effort to control growth and spread of the cancer, as well as to prolong life and maximize function for patients with pancreatic cancer.

Currently, the preferred first-line therapy options for patients with mPAC include the combination therapy of 5-fluorouracil/leucovorin plus oxaliplatin and irinotecan (FOLFIRINOX) and nab-paclitaxel plus gemcitabine, or single-agent gemcitabine (6). FOLFIRINOX was approved by the FDA in 2010 after a large randomized Phase 3 trial showed a significant improvement in OS compared with gemcitabine monotherapy (11.1 versus 6.8 months, hazard ratio for death 0.57; 95%CI 0.45 to 0.73; p <0.001) (23).

There was an improvement in the duration of OS with nab-paclitaxel in combination with gemcitabine (8.5 months) as compared with gemcitabine alone (6.7 months; hazard ratio for death 0.72; 95% CI 0.62 to 0.83; p <0.001). The response rate was significantly higher with nab-paclitaxel plus gemcitabine than with gemcitabine alone (23% [95% CI 19 to 27] versus 7% [95% CI 5 to 10]; p <0.001) (7).

For those patients previously treated with fluoropyrimidine-based therapy, the recommended second-line options are gemcitabine-based therapy, the combination of 5-fluorouracil, leucovorin, and liposomal irinotecan (if no prior irinotecan), or clinical trial participation (6). Second-line gemcitabine plus nab-paclitaxel after FOLFIRINOX failure for patients with advanced pancreatic cancer could be more effective than gemcitabine alone. The ORR was 13.3%, with a median follow-up time of 9.3 months. Median OS and PFS were 7.6 and 3.8 months, respectively (24).

Despite advances in first-line therapy for mPAC, OS remains poor, and second-line treatments remain an unmet medical need; there is currently no optimal treatment for patients whose disease progresses after their initial treatment.

2.3 BENEFIT/RISK ASSESSMENT

The benefit-risk assessment incorporates an evaluation of the key safety and efficacy information that is presently available.

More detailed information about the known and anticipated benefits and risks and reasonably expected adverse events of tusamitamab ravtansine may be found in the Investigator's Brochure (IB). Information regarding known and expected benefits and risks for gemcitabine may be found in prescribing information for gemcitabine.

2.3.1 Risk assessment

Based on the available data, the main important identified risks observed during clinical development of tusamitamab ravtansine are corneal toxicity presenting as keratitis/microcystic keratopathy, which is reversible and manageable with dose delay and dose reduction in some patients. Peripheral neuropathy is an important identified risk in patients previously exposed to neurotoxic drugs. These main important identified and potential risks and respective mitigation strategies are described in Table 2. Other important potential risks were observed in a limited number of patients exposed to tusamitamab ravtasine, and clinical pictures were consistent with a presentation in patients with underlying relevant risk factors. These important potential risks include colitis ([including hemorrhagic], mainly in participants with a known history of colitis or gastrointestinal tract conditions), cardiotoxicity (myocardial or conduction abnormalities), hematologic cytopenias, and hepatotoxicity, as well as systemic acute hypersensitivity reactions (including anaphylaxis and local infusion site reactions.

Table 2 - Risk assessment

Main important potential risk	Summary of data/rationale for risk	Mitigation strategy
Keratitis/microcystic keratopathy	**Preclinical:** Mitotic arrest/single cell necrosis was observed in the cornea of the eye in mice and monkeys. In addition, brown discoloration of the cornea associated, microscopically, with minimal dark pigmentation in cornea epithelial cells was noted in monkeys. **Clinical:** Identified as a risk during the dose-escalation process in the TED13751 study; it was the main DLT. In the TED13751 study pooled data: among the 160 patients treated at a dose level of 100 mg/m^2, Q2W, there were 51 patients (31.9%) with a corneal TEAE, of which 13 patients (8.1%) had events ≥ Grade 3. In the TCD15054 study there were 3 patients (50%) reported with a corneal TEAE, of which 1 patient (16.7%) had keratitis and another patient (16.7%) had punctate keratitis.	Careful history and physical examination. The monitoring of patients for ocular toxicities will be done with regular extensive ocular examination. No primary prophylaxis is recommended but prevention of dry eye with artificial tears and avoidance of using contact lenses during the treatment period. Corticosteroids containing ocular drugs in case ocular symptoms occur. Curative action: dose delay and dose reduction in some patients and symptomatic treatment; ophthalmologist follow-up.
Peripheral neuropathy	**Preclinical**: Nerve fiber degeneration was observed in the peripheral nervous system and spinal cord in mice and monkeys. **Clinical**: In the TED13751 study among the 160 patients treated at a dose level of 100 mg/m^2, Q2W, 43 patients (26.9%) had at least one peripheral neuropathy TEAE. In the TCD15054 study, of the 6 patients treated at a dose level of 100 mg/m^2, Q2W, there was 1 patient (16.7%) with peripheral sensory neuropathy.	Close surveillance of any signs and symptoms of peripheral neuropathies. Peripheral neuropathies potentially presenting as signs and symptoms of sensory (paresthesia, dysesthesias, pain, change in proprioception), motor (weakness), and neural dysfunctions. This AE is managed by dose delay/reduction as well as treatment discontinuation in case of Grade 3-4.

DLT = dose-limiting toxicity; Q2W = every 2 weeks; TEAE = treatment-emergent adverse event.

Additional potential risks were observed during preclinical studies and are anticipated to be associated with DM4. At this stage of the clinical development a limited number of patients presented these adverse reactions and the clinical pictures were consistent with a presentation in patients with underlying relevant risk factors. These potential risks included the following:

- Cardiotoxicity (myocardial or conduction abnormalities) in patients with underlying cardiovascular risk factors which are confounding factors.
- Colitis (including hemorrhagic) in patients with a known history of colitis or gastrointestinal tract conditions, which would not be unexpected and is consistent with their underlying pathology.
- Hepatotoxicity in patients with a known history of hepatotoxicity or patients taking medications known to cause hepatotoxicity or patients with a history of liver abnormalities (symptomatic or asymptomatic).

- Hematologic cytopenias in patients with a known history of cytopenias (leucopenia, neutropenia, thrombocytopenia, or anemia) due to previous treatment with cytotoxic drugs.
- Local infusion site reactions.
- Systemic acute hypersensitivity reactions (including anaphylaxis) which is not supported by preclinical data but rather by very rare occurrences in clinical development.

The current data on efficacy and safety obtained in the ongoing studies of tusamitamab ravtansine (TED13751 and TCD15054) support its continued clinical development.

Gemcitabine

Gemcitabine is a nucleoside metabolic inhibitor indicated as a single agent for the treatment of pancreatic cancer. Potential and identified risks associated with gemcitabine in pancreatic cancer are summarized here.

The most common adverse reactions for the single agent (≥20%) are nausea/vomiting, anemia, increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT), neutropenia, increased alkaline phosphatase, proteinuria, fever, hematuria, rash, thrombocytopenia, dyspnea, and edema.

In a Phase 3 study of efficacy and safety of the combination of nab-paclitaxel and gemcitabine as compared to gemcitabine monotherapy in patients with metastatic pancreatic cancer (7), the most commonly reported AEs of Grade 3 or higher severity were neutropenia (nab-paclitaxel/gemcitabine combination therapy, 38%; gemcitabine monotherapy, 27%), fatigue (combination therapy, 17%; monotherapy, 7%), and neuropathy (combination therapy, 17%; monotherapy, 1%). Febrile neutropenia occurred in 3% of patients receiving the combination in this study, as compared to 1% of the patients receiving gemcitabine alone.

Safety profile for the combinationof tusamitamab ravtansine with gemcitabine

Potentially overlapping risks associated with tusamitamab ravtansine and gemcitabine treatment are the following:

- hematologic cytopenias (anemia, neutropenia, or thrombocytopenia)
- hepatotoxicity (increased ALT, AST, or alkaline phosphatase)

Given the risks of adverse effects including neutropenia, anemia, and infection associated with paclitaxel, the combination of tusamitamab ravtansine with gemcitabine may represent a treatment regimen with an improved safety profile as compared to the approved combination of paclitaxel and gemcitabine.

2.3.2 Benefit assessment

Based on the current data obtained in the ongoing monotherapy studies of tusamitamab ravtansine (TED13751 and TCD15054), the perceived balance between the anticipated benefits and the reported risks of tusamitamab ravtansine in the treatment of advanced malignancies is acceptable and supports the continued clinical development of the agent in other indications, such as mBC

and mPAC, that express CEACAM5 on tumor cells and are historically known to be sensitive to antitubulin agents, which are associated with significant toxicity.

2.3.3 Overall benefit:risk conclusion

Considering the measures taken to minimize risks to participants in this study, the important identified and potential risks observed in association with tusamitamab ravtansine and gemcitabine are justified by the anticipated benefits that may be afforded to participants with mBC and mPAC. To date, the important risks for tusamitamab ravtansine are considered manageable based on the risk minimization measures currently utilized in the clinical studies in conjunction with Sanofi routine pharmacovigilance activities.

3 OBJECTIVES AND ENDPOINTS

Table 3 - Objectives and endpoints

Objectives	Endpoints
Primary	
• For Cohort A, Cohort B, and Cohort C Part 2: To assess the antitumor activity of tusamitamab ravtansine in mBC and tusamitamab ravtansine monotherapy and in combination with gemcitabine in mPAC	• Objective Response Rate (ORR) of tusamitamab ravtansine, defined as the 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
• For Cohort C Part 1: Confirmation of the recommended tusamitamab ravtansine dose when administered in combination with gemcitabine	• Incidence of dose-limiting toxicites (DLTs) in the 28 Day DLT observation period (Cycle 1)
Secondary	
• To assess the safety and tolerability of tusamitamab ravtansine administered as monotherapy and in combination with gemcitabine	• Incidence of participants with treatment-emergent adverse events (TEAEs), serious adverse events (SAEs) and laboratory abnormalities according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0
• To assess other efficacy parameters of tusamitamab ravtansine administered as monotherapy and in combination with gemcitabine	• Progression-free survival (PFS), defined as the time from the date of first tusamitamab ravtansine administration to the date of the first documented disease progression or death due to any cause, whichever comes first • Disease control rate (DCR), defined as the percentage of participants who have achieved confirmed CR, confirmed PR or stable disease as per RECIST v1.1 • Duration of response (DOR), defined as the time from first documented evidence of confirmed CR or confirmed PR until progressive disease determined per RECIST v1.1 or death from any cause, whichever occurs first
• To assess the immunogenicity of tusamitamab ravtansine	• Incidence of participants with antitherapeutic antibodies (ATAs) against tusamitamab ravtansine
• To assess the pharmacokinetics (PK) of tusamitamab ravtansine and gemcitabine when given in combination	• Pharmacokinetic parameters of tusamitamab ravtansine and gemcitabine
Tertiary/exploratory	
• To explore CEACAM5 expression on circulating tumoral cells (CTCs)	• CEACAM5 expression assessment on CTCs from participants with positive CEACAM5 expression on tumor tissue
• To explore modulations of circulating CEA as a potential pharmacodynamics biomarker of response to tusamitamab ravtansine treatment and to evaluate circulating CEA levels at prescreening	• Circulating CEA at prescreening, baseline and during the treatment period
• To assess the relationship between the tumor mutation profiles detected in the circulating free DNA (cfDNA) at baseline with efficacy outcome	• Mutation analysis for tumor cfDNA at baseline

Objectives	Endpoints
• To explore potential sets of biomarkers from tumor DNA and RNA analyses, beside target expression, as potential biomarkers of response to tusamitamab ravtansine treatment	• Biomarker annotation for tumor DNA and RNA at baseline

3.1 APPROPRIATENESS OF MEASUREMENTS

Each of the efficacy and safety assessments chosen for use in this study are considered well established and relevant in an oncology study setting.

In addition, suitable steps have been built into each of these assessments to ensure their reliability and accuracy and to minimize any risks to participant safety.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a Phase 2, open-label, multi-cohort, multi-center study assessing the efficacy (antitumor activity), safety, and immunogenicity of tusamitamab ravtansine in the treatment of participants with mBC (Cohort A [monotherapy]), mPAC (Cohort B [monotherapy] and Cohort C [in combination with gemcitabine]) with CEACAM5-positive tumors (defined as CEACAM5 IHC intensity ≥2+ in ≥50% of tumor cells).

Treatment allocation will be performed using an IRT. After being screened, the eligible participants will receive 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 Cohort A and B, participants will receive a tusamitamab ravtansine loading dose at 170 mg/m² on Day 1 of Cycle 1, followed by 100 mg/m² Q2W from Cycle 2 and in all other cycles.

In Cohort C, each treatment cycle will be 28 days (4 weeks). Cohort C will comprise 2 parts:

Part 1 (Safety Run-In): In Part 1, participants will receive a tusamitamab ravtansine loading dose at 170 mg/m² on Day 1, followed by 100 mg/m² every 2 weeks (Q2W); participants also will receive gemcitabine 1000 mg/m^2 on Day 1, Day 8, and Day 15 every 4 weeks (Q4W). In the case that it is decided to reduce the initial loading dose of tusamitamab ravtansine to DL-1 (Table 4), a tusamitamab ravtansine loading dose of 135 mg/m^2 will be administered to participants on Day 1 of Cycle 1.

Table 4 - Dose levels for Part 1 (safety run-in)

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

BSA = body surface area; DL -1=dose level -1; Q2W = every 2 weeks; Q4W = every 4 weeks.
For participants with a BSA >2.2 m², the tusamitamab ravtansine dose will be calculated based on a BSA of 2.2 m².

The starting dose for tusamitamab ravtansine is selected as the maximum tolerated dose (MTD) used in studies evaluating tusamitamab ravtansine as loading-dose monotherapy. Enough participants will be enrolled in Part 1 to achieve 3 to 12 participants evaluable for DLTs to confirm the recommended dose. The tolerability of the combination is assessed in Part 1 according to the algorithm illustrated in Figure 1. The DLT observation period is the first cycle (approximately 28 days). A DLT-evaluable participant must have completed 1 cycle of treatment or have been discontinued from study treatment because of a DLT; DLT-nonevaluable participants will be replaced. A minimum delay of 1 week is required between the initial dose in the first participant treated in a DL cohort and dosing of the next 2 participants treated at the same DL.

In Part 2 of Cohort C, the recommended dose confirmed in Part 1 will be evaluated for activity in 24 to 27 additional participants. A total of 30 participants, including participants treated at the recommended dose in Part 1, will be evaluated for activity.

The expected duration of study treatment for participants may vary, based on the progression date and cohort; the median expected duration of the study per participant is estimated to be 8 months for Cohorts A and C and 6 months for Cohort B (up to 1 month for screening, a median of 4 or 2 months for treatment in Cohorts A/C and Cohort B, respectively, a median of 1 month for EOT, and a follow-up visit 90 days after the last IMP administration).

Serious adverse events/AESIs (regardless of relationship with study treatment) and IMP-related AEs ongoing at the end of study treatment, and any new IMP-related AEs/SAEs/AESIs will be followed until resolution or stabilization (defined as an event ongoing without any change for at least 3 months). A safety follow-up visit will be performed 90 days after the last IMP administration. If ongoing IMP-related AEs/SAEs/AESIs are resolved or stabilized, no further safety follow-up visit will be needed, otherwise an on-site follow-up visit will be performed every 12 weeks.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The efficacy and the safety of tusamitamab ravtansine will be explored in indications for which the tumor expresses CEACAM5 and which are also known to be sensitive to antitubulin agents such as mBC and PAC.

The prevalence of high CEACAM expression (defined as ≥2+ in intensity involving at least 50% of the tumor cells) is 10% in all mBC types in which no high expression was identified in the primary tumors, 14% in TNBC, and 15% in pancreatic cancer.

Assuming a prescreening failure rate of 90% for Cohort A, 85% for Cohort B, and 58% for Cohort C, and a screening failure rate of 20% for the 3 cohorts, approximately 440 participants for Cohort A, 242 participants for Cohort B, and 90 participants for Cohort C will be prescreened to achieve up to approximately 35 treated participants evaluable for activity (at least 1 postbaseline tumor assessment, early progression, or death due to progressive disease) in Cohort A, 29 treated participants evaluable for activity in Cohort B, and 30 treated participants evaluable for activity in Cohort C.

An interim analysis will be performed when the first 15 treated evaluable participants in Cohort C have had at least 2 postbaseline tumor assessments, experienced confirmed objective response, or have discontinued the study for any reason. For participants with 2 postbaseline tumor assessments and occurrence of response at the second postbaseline tumor assessment, the confirmatory assessment will also be included. For Cohort C, if 1 or 0 confirmed responses are observed among these first 15 treated participants, the cohort will be closed. Once 15 participants have been treated, the enrollment may be paused until a decision regarding the interim analysis can be made.

4.3 JUSTIFICATION FOR DOSE

In the main dose-escalation phase of the first-in-human study TED13751 exploring 5 to 150 mg/m^2 tusamitamab ravtansine doses administered once every 2 weeks, the recommended dose was determined to be 100 mg/m^2 administered every 2 weeks. A cohort of heavily pretreated NSQ NSCLC patients with CEACAM5-positive tumors at the membrane (≥2+ in intensity involving at least 50% of the tumor cell population) have been treated with tusamitamab ravtansine at the recommended dose of 100 mg/m² every 2 weeks. The 64 treated patients showed encouraging antitumor activity associated with a response rate of 20.3% (95% CI: 12.27%-31.71%); 28 (43.8%) had stable disease. An escalation bis cohort using a loading dose is ongoing. The recommended dose is 170 mg/m^2 at Cycle 1 Day 1 followed by 100 mg/m^2 from Cycle 2 and will be used in Cohorts A and B in this study. The increase of the initial exposure at Cycle 1 may increase the efficacy.

For Cohort C, the starting dose of tusamitamab ravtansine to be administered in combination with gemcitabine will be 170 mg/m² at Cycle 1 Day 1 followed by 100 mg/m^2 Q2W. If DLT is observed and after discussion with the study committee, the tusamitamab ravtansine dose may be decreased to 135 mg/m² at Cycle 1 Day 1 followed by 100 mg/m^2 Q2W. The rules for this decision are described in Section 6.5.1.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he/she has completed all phases of the study including the EOT visit and the Follow-Up visit approximately 90 days after the last IMP administration.

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the Schedule of Activities (SoA; Section 1.3) for the last participant in the trial globally.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 INCLUSION CRITERIA

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

I 01. Participant must be at least 18 years of age (or country's legal age of majority if >18 years), at the time of signing the informed consent.

Type of participant and disease characteristics

I 02. Participants with at least one measurable lesion according to the RECIST v1.1 criteria that has not been irradiated (ie, newly arising lesions in previously irradiated areas are accepted). The lesion must be ≥10 mm in the longest diameter (except lymph nodes, which must have short axis ≥15 mm) with computed tomography (CT) (preferred) or magnetic resonance imaging (MRI) scans.

I 03. Participants with ECOG performance status 0 to 1.

I 04. Evidence of metastatic disease.

Cohort A: mBC

I 05. Histological or cytologic diagnosis of breast cancer.

I 06. Expression of CEACAM5 as demonstrated prospectively by a centrally assessed IHC assay of ≥2+ in intensity involving at least 50% of the tumor cell population in archival or fresh tumor sample at the metastatic site (mandatory) including distant lymph nodes. At least 5 fresh cut slides of formalin-fixed paraffin embedded (FFPE) tumor tissue sectioned at a thickness of 4 to 5 µm are required. Cell collections (eg, from pleural effusion) processed as FFPE blocks are acceptable. If less material is available, the participant could still be considered eligible after discussion with the Sponsor, who may assess and confirm that the available material is sufficient for key evaluations.

I 07. Have received at least 2 prior cytotoxic chemotherapy regimens for non-TNBC tumor type or at least 1 for TNBC tumor type but not more than 4 in the locally recurrent or metastatic setting.

I 08. Participants with non-TNBC tumor type (either at primary diagnostic or at metastatic site) is defined as any estrogen receptor (ER) and/or progesterone receptor positive (≥1% tumor staining by IHC) and/or HER2 positive (IHC [3+] or IHC [2+] and in situ hybridization [ISH] positive based on single-probe average HER2 copy number ≥6.0 signals/cell or dual-probe HER2/CEP17 ratio ≥2.0 with an average HER2 copy number ≥4.0 signals/cell)

disease status. Participants must be no longer eligible for hormonal therapy or HER2-targeted therapy.

I 09. Participants with TNBC tumor type (either at primary diagnostic or at metastatic site) is defined as ER/Progesterone receptor negative (<1% tumor staining by IHC), and HER2 nonoverexpressing by IHC (0, 1+) or ISH-negative based on single-probe average HER2 copy number <4.0 signals/cell or dual-probe HER2/CEP17 ratio <2.0 with an average HER2 copy number <4.0 signals/cell.

Note:

1. Adjuvant/neo-adjuvant chemotherapy will be counted as a prior chemotherapy for metastatic/recurrent disease if the participant had a progression/recurrence within 6 months after completion of the treatment.
2. Prior hormonal, biologic (eg, bevacizumab) or immunotherapy, without a cytotoxic agent, are allowed and are not counted as a line of therapy.
3. A chemotherapy line in advanced/metastatic disease is an anti-cancer regimen that contains at least 1 cytotoxic chemotherapy agent and was discontinued due to progression. If a cytotoxic chemotherapy regimen was discontinued for a reason other than disease progression then this regimen does not count as a "prior line of chemotherapy" unless this regimen was discontinued after at least 2 cycles of treatment.

Cohorts B and C: mPAC

I 10. Have confirmed diagnosis of pancreatic ductal adenocarcinoma.

I 11. Expression of CEACAM5 as demonstrated prospectively by a centrally-assessed IHC assay of ≥2+ in intensity involving at least 50% of the tumor cell population in archival tumor sample (or, if not available, a fresh biopsy sample). At least 5 fresh cut slides of FFPE tumor tissue sectioned at a thickness of 4 to 5 µm are required. Cell collections (eg, from pleural effusion) processed as FFPE blocks are acceptable. If less material is available, the participant could still be considered eligible after discussion with the Sponsor, who may assess and confirm that the available material is sufficient for key evaluations.

Cohort B: mPAC

I 12. Cohort B: Have documented radiographic progression or documented intolerance after at least 1 prior systemic chemotherapy line which included either gemcitabine (or relapsed within 6 months of completion of gemcitabine adjuvant therapy) or a 5-fluorouracil based regimen (including capecitabine) but no more than 2 prior chemotherapy lines for locally advanced/metastatic disease.

Sex

I 13. All (male and female)

Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

a) Male participants

Male participants are eligible to participate if they agree to the following during the intervention period and for at least 4 months after the last dose of tusamitamab ravtansine, and at least 6 months after the last dose of gemcitabine:

- Refrain from donating sperm

Plus either:

- Be abstinent from heterosexual or homosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

  OR

- Must agree to use contraception/barrier as detailed below
  - Agree to use male condom when engaging in any activity that allows for passage of ejaculate to another person

b) Female participants

- A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:
  - Is not a woman of childbearing potential (WOCBP)
    - OR
  - Is a WOCBP and agrees to use a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, as described in Appendix 4 of the protocol during the intervention period and for at least 7 months after the last dose of study intervention and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period.
  - A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) before the first dose of study intervention.
- Additional requirements for pregnancy testing during and after study intervention are located in Appendix 2 (Section 10.2) of the protocol.
- The Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

I 14. Capable of giving signed informed consent as described in Appendix 1 of the protocol which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

Criterion added in amended protocol (only for participants in Cohort C)

I 15. Have documented radiographic progression or documented intolerance after 1st line fluoropyrimidine-containing chemotherapy (or relapsed within 6 months of completion of chemotherapy as adjuvant therapy) for locally advanced/metastatic disease.

5.2 EXCLUSION CRITERIA

Participants are excluded from the study if any of the following criteria apply:

Medical conditions

E 01. Medical condition requiring concomitant administration of a medication with a narrow therapeutic window, that is metabolized by cytochrome P450 (CYP450) (see Appendix 10; Section 10.10), and for which a dose reduction cannot be considered.

E 02. Medical conditions requiring concomitant administration of strong CYP3A inhibitor (see Appendix 10; Section 10.10), unless it can be discontinued at least 2 weeks before the first administration of study intervention.

E 03. Life expectancy less than 3 months.

E 04. Untreated brain metastases or history of leptomeningeal disease. Participants with previously treated brain metastases may participate provided that:

- they are stable (ie, without evidence of progression by imaging for at least 4 weeks prior to the first administration of study treatment, and any neurologic symptoms have returned to baseline);
- there is no evidence of new or enlarging brain metastases;
- and the participant does not require any systemic corticosteroids to manage brain metastases within 3 weeks prior to the first dose of study intervention.

E 05. Significant concomitant illness, including any severe medical condition that, in the opinion of the Investigator or Sponsor, would impair the participant's participation in the study or interpretation of the results.

E 06. History within the last 3 years of an invasive malignancy other than the one treated in this study, with the exception of resected/ablated basal or squamous-cell carcinoma of the skin or carcinoma in situ of the cervix, or other local tumors considered cured by local treatment.

E 07. History of known acquired immunodeficiency syndrome (AIDS) related illnesses or known human immunodeficiency virus (HIV) disease requiring antiretroviral treatment, or active hepatitis A, B (defined as either positive HBsAg or positive hepatitis B viral deoxyribonucleic acid [DNA] test above the lower limit of detection of the assay), or C (defined as a known positive hepatitis C antibody result and known quantitative hepatitis C virus [HCV] RNA results greater than the lower limits of detection of the assay) infection. HIV serology will be tested at screening only for participants enrolled in any country where mandatory per local requirements.

E 08. Non-resolution of any prior treatment-related toxicity to < Grade 2 according to NCI-CTCAE v5.0, with the exception of alopecia, vitiligo, or active thyroiditis controlled with hormone replacement therapy (HRT).

E 09. Unresolved corneal disorder or any previous corneal disorder considered by an ophthalmologist to predict higher risk of drug-induced keratopathy.

E 10. Use of contact lenses. Participants using contact lenses who are not willing to stop wearing them for the duration of the study intervention are excluded.

Prior/concomitant therapy

E 11. Concurrent treatment with any other anti-cancer therapy.

E 12. Washout period before the first administration of study intervention of less than 3 weeks or less than 5 times the half-life, whichever is shorter, for prior anti-tumor therapy (chemotherapy, targeted agents, immunotherapy and radiotherapy, or any investigational treatment).

E 13. Any prior therapy targeting CEACAM5.

E 14. Prior maytansinoid DM4 treatment (ADC).

E 15. Any major surgery within the preceding 3 weeks of the first study intervention administration.

Prior/concurrent clinical study experience

E 16. Previous enrollment in this study or current participation in any other clinical study involving an investigational study treatment or any other type of medical research.

Diagnostic assessments

E 17. Poor renal function as defined by serum creatinine >1.5 × upper limit of normal (ULN) or 1.0 to 1.5 × ULN with estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m² as estimated using a modification of diet in renal disease (MDRD) formula.

E 18. Poor hepatic function as defined by total bilirubin >1.5 × ULN (except participants with Gilbert's syndrome, for whom total bilirubin ≤3.0 × ULN with direct bilirubin ≤1.5 × ULN is allowed).

E 19. Poor hepatic function as defined by AST, ALT, or alkaline phosphatase (AP) >2.5 × ULN, except participants with liver metastases for whom AST, ALT, or AP ≤5 × ULN is allowed or participants with bone metastases for whom AP ≤5 × ULN is allowed.

E 20. Poor bone marrow function as defined by neutrophils <1.5 × 10^9/L or platelet count <100 × 10^9/L or hemoglobin <9 g/dL (no blood and blood product transfusion within 2 weeks before screening).

Other exclusions

E 21. Individuals accommodated in an institution because of regulatory or legal order; prisoners or participants who are legally institutionalized.

E 22. Any country-related specific regulation that would prevent the participant from entering the study - see Appendix 8 (Section 10.8) of the protocol for country-specific requirements.

E 23. Participant not suitable for participation, whatever the reason, as judged by the Investigator, including medical or clinical conditions, or participants potentially at risk of noncompliance to study procedures.

E 24. Participants are employees of the clinical study site or other individuals directly involved in the conduct of the study, or immediate family members of such individuals (in conjunction with Section 1.61 of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)-Good Clinical Practice (GCP) Ordinance E6).

E 25. Any specific situation during study implementation/course that may rise ethics considerations.

E 26. Sensitivity to any of the study interventions, or components thereof, or drug or other allergy that, in the opinion of the Investigator, contraindicates participation in the study.

Criterion added in amended protocol (only for participants in Cohort C)

E 27. Any previous systemic therapy with taxane or gemcitabine (for Cohort C only).

5.3 LIFESTYLE CONSIDERATIONS

No restrictions are required.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure reasons, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) and for whom resolution of the screen failure may not be expected within a reasonable time frame, the screen failure will be recorded. Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened participants should be assigned a different participant number to the initial screening, and all the screening procedures will be repeated and entered in the screening visit pages. In case the participant is a temporary screen failure and requires prolongation of the screening period, there is no need to have participant re-consent (ie, new ICF signed) if the participant finally participates in the trial. However, if the reason for the temporary screen failure is one that might have altered the participant's initial given agreement to participate, the Investigator should ensure the willingness of the participant to continue or redo some screening procedures and his/her participation to the trial. This oral agreement should be documented in the participant's chart. All the tests out of protocol window should be repeated and entered to the additional pages. The participants who will be rescreened after this period need to resign new screening ICF; there will be no re-prescreening for CEACAM5 expression and the initial value will be applicable, with respect to maximum allowed window for prescreening.

5.5 CRITERIA FOR TEMPORARILY DELAYING ENROLLMENT

During a regional or national emergency declared by a governmental agency, the Investigator/site should assess the site's capacity to conduct procedures for a new participant to be enrolled into the study before initiating any screening procedures. Site capacity also should be ensured before randomization of a participant. If the site is unable to adequately follow protocol mandated procedures, contingency measures proposed in Appendix 9 (Section 10.9) should be applicable to prescreening/screening/enrollment/administration of study treatment.

6 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1 STUDY INTERVENTION(S) ADMINISTERED

Table 5 - Overview of study interventions administered

Intervention label	tusamitamab ravtansine (SAR408701)	gemcitabine
Intervention name	tusamitamab ravtansine (SAR408701)	gemcitabine
Type	Drug	Drug
Dose formulation	Concentrated solution for IV	lyophilized powder for reconstitution for IV[a]
Unit dose strength(s)	5 mg/mL	not applicable
Dosage level(s)	Loading dose 170 mg/m^2 (or 135 mg/m^2 only for Cohort C) over 1 hour 30 minutes on Day 1 of Cycle 1 Other doses 100 mg/m^2 Q2W For participants with a BSA >2.20 m^2, the dose will be calculated based on a BSA of 2.20 m^2	1000 mg/m^2 over 30 minutes on Day 1, Day 8, and Day 15, Q4W
Route of administration	IV infusion[b]	IV infusion[b]
Use	experimental	experimental
IMP or NIMP	IMP	IMP
Packaging and labeling	Supplied in a 30 mL glass vial containing 125 mg/25 mL tusamitamab ravtansine (SAR408701). Packaging is in accordance with the administration schedule. The content of the labeling at vial and box level is in accordance with the local regulatory specifications and requirements.	Per specifications for locally available/marketed source, where local sourcing is possible
Current/Former name(s) or alias(es)	Not applicable	As per locally marketed formulation

a. For locally sourced IMP, if the recommended formulation is not available. Local approved formation can be used after confirmed with the Sponsor.

b. Infusion via a central line is preferred (line will be flushed before infusion), if available. Prior to dosing, each participant's dose will be individually prepared by the study pharmacist and labeled with protocol number, participant number, and treatment description.

Table 6 - Arms and associated interventions

Arm name	Cohort A (mBC)	Cohort B (mPAC)	Cohort C (mPAC)
Associated interventions (intervention label[s])	Tusamitamab ravtansine (SAR408701)	Tusamitamab ravtansine (SAR408701)	Tusamitamab ravtansine (SAR408701) + gemcitabine

After the study cut-off date for the secondary efficacy endpoints (see Section 9.3.1), participants with observed clinical benefit who are still receiving study treatment can continue on study treatment.

Study intervention will be administered until documented disease progression, unacceptable toxicity, new anti-cancer therapy initiation, or the participant's or Investigator's decision to stop the treatment.

Noninvestigational medicinal product (NIMP): Premedication for tusamitamab ravtansine

Tusamitamab ravtansine (SAR408701) has a potential risk of infusion-related reaction and premedication should be used. All the drugs used as premedication will be entered to the concomitant premedication page.

Premedication with a histamine H1 antagonist (oral diphenhydramine 50 mg or equivalent [eg, dexchlorpheniramine] given approximately 15 minutes to 1 hour before tusamitamab ravtansine (SAR408701) administration depending on the administration form - IV or oral [15 minutes prior for IV and 1 hour prior for oral]) is required for all participants before the administration of tusamitamab ravtansine (SAR408701). If a participant has experienced an infusion reaction following previous tusamitamab ravtansine (SAR408701) administration, premedication will also include dexamethasone 10 mg IV for future infusions. If the participant does not experience any hypersensitivity reactions after 4 cycles, the premedication can be discontinued at the discretion of the Investigator.

Premedication for gemcitabine: Antiemetic preventive therapy must be given according to ASCO guidelines and the local practice. Gemcitabine is known as a low-emetic-risk antineoplastic agent. According to ASCO anti-emetics guidelines updated on May 6th, 2020, adults treated with low-emetic-risk antineoplastic agents should be offered a single dose of a 5-HT3 receptor antagonist or a single 8◦mg dose of dexamethasone before antineoplastic treatment (8).

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

A complete description of the IMPs and their proper handling will be provided in a Pharmacy Manual available at the investigational site.

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

4. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
5. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
6. Further guidance and information for the final disposition of used and unused study interventions are provided in the pharmacy manual and/or monitoring plan.

Any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) must be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure (see Section 8.3.8).

A potential defect in the quality of IMP may be subject to initiation of a recall procedure by the Sponsor. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall the IMP and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP to a third party, allow the IMP to be used other than as directed by this clinical trial protocol, or dispose of IMP in any other manner.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Not Applicable.

6.4 STUDY INTERVENTION COMPLIANCE

When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.

When participants are dosed at the site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The person responsible for drug dispensing is required to maintain adequate records of the IMPs. These records (eg, drug movement form) include the date the IMPs are received from the Sponsor, dispensed to the participant and destroyed or returned to the Sponsor. The packaging batch number (IP number) and the treatment number on the vial must be recorded on the drug accountability form. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the case report form (CRF). Deviation(s) from the prescribed dosage regimen should be recorded in the electronic case report form (eCRF). The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.5 DOSE MODIFICATION

6.5.1 Determination of recommended dose for Cohort C

During Part 1 of Cohort C, recommended dose of tusamitamab ravtansine in combination with gemcitabine will be determined according to the DLTs observed in participants according to the algorithm shown in Figure 1:

- If 0/3 participants experiences a DLT at the starting loading dose, the starting loading dose will be RP2D.
- If 1/3 participants experiences a DLT at the starting dose, the next 3 participants of the combination arm will be treated at the same DL to confirm the tolerability of the combination at the starting dose.
  - If ≤1/6 participants treated at the starting dose experiences a DLT, the starting dose will be the RP2D.
  - If ≥2/6 participants treated at the starting dose experience a DLT, the dose will be de-escalated to DL-1 for the next 3 participants of the combination arm.
- If ≥2/3 participants experience a DLT at the starting dose, the dose will be de-escalated to DL-1 for the next 3 participants of the combination arm.
  - If ≤1/3 participants treated at the DL-1 experiences a DLT, the next 3 participants of the combination arm will be treated at the same DL to confirm the tolerability of the combination at DL-1.
    - If ≤1/6 participant treated at the DL-1 experiences a DLT, the DL-1 will be the RP2D.
    - If ≥2/6 participants treated at the DL-1 experience a DLT, an alternative dosage might be considered or the study part may be stopped.
  - If ≥2/3 participants treated at DL-1 experience a DLT, an alternative dosage might be considered or the study part may be stopped.

The tolerability of the combinations will be assessed in 3 to 12 participants depending on DLTs observed. Dose modification and dose schedules are shown in Table 4. The Study Committee will review clinical data regularly during the study (Section 10.1.5). The dosage decision for the combination will be made during this meeting. Definitions of DLTs are provided in Table 7.

Table 7- Dose-limiting toxicities

Hematological abnormalities
Grade 4 neutropenia for 7 or more consecutive days.
Grade 3 to 4 neutropenia complicated by fever (temperature ≥38.5°C on more than 1 occasion) or microbiologically or radiographically documented infection
Grade ≥3 thrombocytopenia associated with clinically significant bleeding requiring clinical intervention
Nonhematological abnormalities
Grade 4 nonhematologic AE
Grade ≥3 keratopathy
In addition, any other AE that the recruiting Investigators and Sponsor deem to be dose limiting, regardless of its grade, may also be considered as DLT.

Abbreviations: AE = adverse event; DLT = dose-limiting toxicity.

All AEs specified in Table 7 occurring during the first cycle of treatment, unless due to disease progression or to a cause obviously unrelated to IMP, will be considered DLTs. During the DLT evaluation period in the safety run-in part, IMPs can be delayed but not omitted; the DLT evaluation period will be prolonged in such cases. The duration of the DLT observation period will be longer for a participant who delays initiation of Cycle 2 due to a treatment-related AE for which the event's duration would determine whether the AE meets the definition of a DLT. The DLTs will be confirmed by the Study Commitee. The severity of AEs will be assessed according to NCI CTCAE Version 5.0. Causal relationships are to be determined by the Investigator.

6.5.2 Individual dose adjustment/dose delay: Cohort A, Cohort B and Cohort C Part 2

Dose adjustment and/or cycle delays are permitted in case of adverse reactions. In case of toxicity, cycle delays and dose modifications should be implemented according to Appendix 6 (Section 10.6). Every effort will be made to administer the full dose regimen and maximize dose intensity.

Dose adjustments will be made according the worst grade of adverse reaction observed within a cycle. If a participant experiences several adverse reactions and there are conflicting recommendations, the most conservative dose adjustment recommended should be followed.

Administration of the study treatment will be discontinued in the event of a TEAE that persists despite appropriate dose modifications or any other AE that, in the opinion of the Investigator, warrants discontinuation.

Dose modifications different from those stated in the protocol should only be made in consultation with the Sponsor unless required for immediate participant safety.

All changes to study treatment administration must be recorded in the eCRF.

In the event of neutropenia, therapeutic granulocyte colony-stimulating factor (G-CSF) should be administered according to the current American Society of Clinical Oncology (ASCO) guidelines (25). In the event of neutropenia or febrile neutropenia, prophylactic G-CSF should be started, and in the event of a second episode beside prophylactic G-CSF, the dose should be reduced

(Section 10.6). The acceptable treatment window is ±2 days for Cohort A and B and ±3 days for Cohort C.

One dose reduction of tusamitamab ravtansine and 2 dose reductions of gemcitabine are allowed during the conduct of the study for safety reasons. If a second dose reduction of tusamitamab ravtansine is considered necessary, this will be decided on a case-by-case basis following discussion with the Sponsor. In the event of a dose reduction, the study intervention will be administered as shown in Table 8. Dose delays are allowed for safety management. Retreatment of participants that requires more than a 1 month dose delay must be justified following a case-by-case risk benefit assessment (see Section 6.5.3). See Table 15 in Appendix 10.6 for guidance on dose modification or discontinuation.

Table 8 - Dose modification for toxicity

Drug name	Dose	1st dose reduction	2nd dose reduction
tusamitamab ravtansine[a]	100 mg/m² Q2W	80 mg/m² Q2W	(not permitted)
gemcitabine	1000 mg/m²	800 mg/m²	600 mg/m²

a Dose modification is applicable from Cycle 2. The loading dose will remain 170 mg/m² (or 135 mg/m² in Cohort C).

If appropriate, and if in the opinion of the Investigator, the toxicity is related to 1 of the 2 drugs (tusamitamab ravtansine or gemcitabine) instead of the combination, and more than 1 cycle delay is needed, the unrelated drug can be continued, and the related drug may be omitted if the delay exceeds 7 days, upon discussion with the Sponsor, and administration resumed at following recovery from the toxicity to Grade ≤1. If the toxicity is related to the combination, both agents should be reduced (if applicable), omitted, or definitively discontinued according to the recommended dose modifications (Section 10.6). If 1 of the 2 drugs (tusamitamab ravtansine or gemcitabine) is prematurely permanently discontinued, the other drug can be continued until disease progression.

6.5.3 Retreatment criteria

All participants entered into the study will be treated at Day 1 of each cycle, and participants in Cohort C, also at Day 8 and Day 15 of each cycle. A participant may receive additional study interventions if he/she meets the retreatment criteria as determined by the Investigator and agrees to be retreated.

For the retreatment of all participants on Day 1 (or, for Cohort C, on Day 15) of each subsequent cycle, the participant must meet all of the following criteria to be eligible for retreatment:

- Neutrophils count $\geq 1.5 \times 10^9$/L
- Platelets $\geq 100 \times 10^9$/L
- Hemoglobin ≥9 mg/dL
- Total bilirubin ≤1.5 × ULN (except participants with Gilbert's syndrome, for whom total bilirubin ≤3.0 × ULN with direct bilirubin ≤1.5 × ULN is allowed)
- AST, ALT ≤2.5 × ULN or ≤5 × ULN in case of documented liver metastasis

- No IMP-related toxicity Grade >1 (except for alopecia) or baseline severity.

For the treatment of participants on Day 8 of each cycle in Cohort C, the participant must meet all of the following criteria to be eligible for retreatment:

- Neutrophil count $\geq 1 \times 10^9$/L
- Platelets $\geq 75 \times 10^9$/L

6.6 CONTINUED ACCESS TO INTERVENTION AFTER THE END OF THE STUDY

After the end of the study (see definition in Section 4.4), interventions should be decided by the Investigator per clinical practice.

6.7 TREATMENT OF OVERDOSE

The Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the Investigator should:

1. Contact the Sponsor or Sponsor representative(s) immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities.
3. Obtain a plasma sample for PK analysis if requested by the Sponsor or Sponsor representative(s) (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Sponsor or Sponsor representative(s) based on the clinical evaluation of the participant.

6.8 CONCOMITANT THERAPY

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates

The Sponsor or Sponsor representative(s) should be contacted if there are any questions regarding concomitant or prior therapy.

Concomitant medications should be kept to a minimum during the study. However, if these are considered necessary for the participant's welfare and are unlikely to interfere with the IMP, they may be given at the discretion of the Investigator and recorded in the eCRF. Concomitant

medication will be recorded in the eCRF from 28 days prior to the first study intervention administration, before every cycle during the study treatment period, and for up to 30 days after the final dose of study intervention. Once the participant has withdrawn from study treatment, concomitant medication should only be recorded if used to treat new or unresolved study treatment-related adverse events.

Concomitant medication may be considered on a case-by-case basis by the Investigator, in accordance with the following guidelines:

- Palliative radiotherapy may be given for control of pain for palliative intents. Approval should be obtained from the Sponsor prior to initiating treatment if palliative radiotherapy is being considered, and prior to resuming therapy on the study. The irradiated area should be as small as possible and should never involve more than 20% of the bone marrow in any given 3-week period. In all such cases, the possibility of tumor progression should be ruled out by physical and radiological assessments of the tumor. If the only evaluable lesions are to be irradiated, the participant will stop the study intervention. The irradiated area cannot be used as a parameter for response assessment.
- Any background therapy taken by the participant for concomitant illnesses other than cancer (eg, HRT, statin, antihypertensive medication) is allowed.
- Supportive treatment as medically indicated for the participant's well-being may be prescribed at the Investigator's discretion. Every medication or treatment taken by the participant during the trial and the reason for its administration must be recorded on the eCRF.

The following concomitant treatments are not permitted during this study:

- Concurrent treatment with other investigational drugs.
- Concurrent treatment with any other anti-cancer therapy not specified in the protocol, including immunotherapy, hormonal therapy, targeted therapy or biological therapies.
- The primary prophylactic use of Granulocyte-Colony Stimulating Factor is not allowed during the first cycle but secondary prophylaxis or therapeutic administration is allowed.
- The use of prophylactic erythropoietin during the first cycle.
- Participants treated or intended to be treated with drugs presented as CYP substrates with a narrow therapeutic range should be carefully monitored (See Section 10.10).
- Concomitant use of strong CYP3A inhibitors should be avoided from 2 weeks before tusamitamab ravtansine administration up to the last tusamitamab ravtansine administration (See Section 10.10).
- The use of contact lenses will not be permitted during the study treatment period.

6.8.1 Rescue medicine

Not applicable.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

7.1.1 Definitive discontinuation

The study intervention should be continued until the confirmed progression of disease whenever possible. Permanent study intervention discontinuation before disease progression should be discussed with the Investigator. Any study intervention discontinuation must be fully documented in the eCRF.

If study intervention is permanently discontinued, the participant will remain in the study for tumor assessments as described in Section 8.1.

Study intervention should be discontinued in any of the following cases:

- At the participant's request, at any time and irrespective of the reason (consent's withdrawal), or at the request of their legally authorized representative. "Legally authorized representative" is considered to be an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective participant to the patient's participation in the procedure(s) involved in the research.
- If, in the Investigator's opinion, continuation of the study treatment would be detrimental to the participant's well-being, such as:
  - Unacceptable AE.
  - Confirmed disease progression.
  - Poor compliance to the study protocol.
  - Other, such as concurrent illness, that prevents further administration of study intervention.
- Participant is lost to follow-up.
- Sponsor decision to discontinue the study.

See Appendix 6 (Section 10.6) for more details on discontinuation.

See the SoA (Section 1.3) for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

Handling of participants after definitive intervention discontinuation

Participants will be followed-up according to the study procedures specified in this protocol up to the scheduled date of study completion, or up to recovery or stabilization of any AE/SAE/AESI to be followed-up as specified in this protocol, whichever comes last.

If possible, and after the definitive discontinuation of intervention, the participants will be assessed using the procedure normally planned for the last dosing day with the IMP including tumor assessment, safety laboratory test, and immunogenicity sample, if appropriate.

All cases of definitive intervention discontinuation must be recorded by the Investigator in the appropriate pages of the eCRF when considered as confirmed.

7.1.2 Temporary discontinuation

Temporary intervention discontinuation may be considered by the Investigator because of suspected AEs or disruption of the clinical trial due to a regional or national emergency declared by a governmental agency (Appendix 9; Section 10.9). For all temporary intervention discontinuations, the duration should be recorded by the Investigator in the appropriate pages of the eCRF.

7.1.2.1 Rechallenge

Reinitiation of intervention with the IMP will be done under close and appropriate clinical/and or laboratory monitoring once the Investigator has considered according to his/her best medical judgment that the responsibility of the IMP(s) in the occurrence of the concerned event was unlikely and if the retreatment criteria for the study are still met (refer to Section 6.5.1).

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 9 (Section 10.9).

During a regional or national emergency declared by a governmental agency, reinitiation of IMP after temporary discontinuation can occur only once the Investigator has determined, according to his/her best judgment, that the participant would likely benefit from continued study treatment, and the IMP(s) was unlikely to contribute to the occurrence of an event of epidemic (eg, COVID-19 [COVID-19]). The Investigator should discuss the restart of IMP after prolonged cycle delay with the Sponsor or Sponsor's representative(s).

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an EOT visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

If participants no longer wish to take the IMP, they will be encouraged to remain in the study.

The Investigators should discuss with them key visits to attend. The value of all their study data collected during their continued involvement will be emphasized as important to the public health value of the study.

Participants who withdraw from the study intervention should be explicitly asked about the contribution of possible AEs to their decision, and any AE information elicited must be documented.

All study withdrawals should be recorded by the Investigator in the appropriate screens of the eCRF and in the participant's medical records. In the medical record, at least the date of the withdrawal and the reason should be documented.

In addition, a participant may withdraw his/her consent to participate in the study. Withdrawal of consent for intervention should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for non-participant contact follow-up, eg, medical record checks. The site should document any case of withdrawal of consent.

Participants who have withdrawn from the study cannot be reallocated (treated) in the study. Their inclusion and intervention numbers must not be reused.

7.3 LOST TO FOLLOW UP

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1 (Section 10.1).

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- During the screening period demography and medical/surgical/disease history will be evaluated. Demography includes age, gender, race, and ethnicity. Medical/surgical/disease history includes histologic types, stage at diagnosis, disease extent at study entry and specific mutations.
- CEACAM5 expression status (archival or fresh tumor tissue) and circulating CEA will be evaluated during prescreening period after prescreening informed consent is signed. Once the participants are confirmed to have positive CEACAM5 tumors, they can continue with screening procedures.
- After the study cut-off date for the primary analysis (see Section 9.3.1), participants will continue to undergo all assessments as per the SoA (Section 1.3).

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 9 (Section 10.9).

8.1 EFFICACY ASSESSMENTS

All efficacy endpoints are based on tumor assessments. The schedule of tumor assessments is provided in the SoA (Section 1.3). Tumor assessments will be done at screening, and then every 8 weeks (±7 days) until EOT, and then every 12 weeks until progressive disease, new anti-cancer therapy, death, withdrawal of participant's consent, or study cut-off date for secondary efficacy endpoints, whichever comes first. The scheduled assessment time point will not be modified in the event of a cycle delay.

The tumor assessment method per RECIST v1.1 is detailed in Section 10.11. Chest, abdominal, pelvic CT-scan or MRI and any other examinations as clinically indicated will be performed to assess disease status. Confirmatory radiological evaluation will be performed at least 4 weeks after initial documentation of response. After IMP discontinuation, tumor assessment should be performed at EOT for participants without imaging performed within the past 4 weeks. Bone CT-scan or MRI and other examinations should be performed if clinically indicated. Brain CT-scan or MRI should be performed at baseline and followed during treatment only for participants with brain lesions at baseline.

Imaging assessments are to be scheduled using the Cycle 1, Day 1 date as the reference for all time points and are not to be scheduled based on the date of the previous imaging time point. Imaging assessment delays to conform to treatment delays are not permitted. The same tumor assessment technique must be used throughout the study for a given lesion/participant.

Objective response rate will be determined by the proportion of participants with confirmed CR or PR. ORR per RECIST v1.1 is the primary endpoint of this study and PFS, DCR, and DOR per RECIST v1.1 are secondary endpoints. Objective response rate will be derived based on Investigator review at each time point at which a response assessment occurred using the RECIST v1.1 (see Section 10.11).

8.2 SAFETY ASSESSMENTS

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1 Physical examinations

- A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, central nervous systems, hepatomegaly, splenomegaly, and lymphadenopathy.
- Height (at screening only) and weight will also be measured and recorded.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- Any new finding or worsening of previous finding should be reported as a new adverse event.

8.2.2 Vital signs

- Temperature and blood pressure will be assessed.
- Blood pressure will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).

8.2.3 Electrocardiograms

- Single 12-lead electrocardiogram (ECG) will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.
- ECG is to be repeated as clinically indicated. This test can be performed before the study intervention administration on the same day or the day before.

8.2.4 Clinical safety laboratory assessments

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition. Laboratory abnormalities are to be recorded as AEs only if they lead to treatment discontinuation and/or dose modification and/or fulfill a seriousness criterion and/or are defined as an AESI.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Sponsor or Sponsor representative(s).
  - If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified.
  - All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the SoA.
  - If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

8.2.5 Pregnancy testing

- Refer to Section 5.1 for pregnancy testing criteria; the Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a female participant with an early undetected pregnancy.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted at monthly intervals during intervention (at study visits and if needed, at home in between visits).
- Pregnancy testing (urine or serum as required by local regulations) must be conducted corresponding with the time frame for female participant contraception in Section 5.1.
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the Investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.

8.2.6 Performance status

Performance status will be evaluated using ECOG scale (26).

8.2.7 Specific ocular test

Standard specific ocular tests include:

- Assessment of ocular/visual symptoms, (ie, blurred vision, photophobia, dry eye, etc)
- Visual acuity
- Slit lamp under dilatation
- Schirmer's test

Standard specific ocular tests are planned at screening and EOT but can also be performed whenever clinically indicated. Assessment of ocular/visual symptoms should be performed at each visit before each study intervention.

In participants with any ocular/visual symptom(s) (eg, blurred vision, photophobia) the complete ocular tests will be repeated at the time of the occurrence of the ocular toxicity, if any, regardless of the grade. Then, visual acuity, slit-lamp examination under dilatation, and Schirmer's test will be repeated once weekly (if not recommended to have less frequent assessments by the ophthalmologist based on lesion characteristics) until resolution to Grade 1. In case of recurrent ocular toxicity observed in subsequent cycles, visual acuity and slit-lamp examination under dilatation, and Schirmer's test will be performed at the time of the event onset, then weekly until resolution to Grade 1.

8.3 ADVERSE EVENTS (AES), SERIOUS ADVERSE EVENTS (SAES) AND OTHER SAFETY REPORTING

The definitions of adverse events (AEs) and serious adverse events (SAEs) can be found in Appendix 3 (Section 10.3). The definition of AESI is provided in Section 8.3.8. Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

8.3.1 Time period and frequency for collecting AE and SAE information

All AEs and SAEs will be collected from the signing of the screening ICF until the follow-up visit at the time points specified in the SoA (Section 1.3). During prescreening, only AEs related to the fresh biopsy procedure (if applicable) and occurring within 1 month after the fresh biopsy will be recorded in the eCRF.

All SAEs and AESIs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3 (Section 10.3). The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

8.3.2 Method of detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/AESI/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. At the pre-specified study end-date, all SAEs/AESIs and IMP-related AEs (as defined in Section 8.3.8), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 3 (Section 10.3).

8.3.4 Regulatory reporting requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.
- Adverse events that are considered expected will be specified in the reference safety information (refer IB).
- Suspected unexpected serious adverse reactions (SUSARs) are reported to regulatory authorities, Investigators, and IRBs/IECs as follows:
    - For SUSARs that are life-threatening or result in death, reporting is no later than 7 days after first knowledge by the Sponsor, with all relevant follow-up information subsequently reported within an additional 8 days.

- For SUSARs, other than those that are life-threatening or result in death, reporting is no later than 15 days after first knowledge by the Sponsor.

- An Investigator who receives an Investigator safety report describing a SAE, SUSAR or any other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements. It is the responsibility of the Sponsor to assess whether an event meets the criteria for a SUSAR, and therefore, is expedited to regulatory authorities.

8.3.5 Pregnancy

- Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study intervention and until 7 months after the last dose of study intervention.
- If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy of female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner).
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.
- The participant /pregnant female partner will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant /pregnant female partner and the neonate and the information will be forwarded to the Sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former study participants /pregnant female partner, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

8.3.6 Cardiovascular and death events

Cardiovascular events will be treated as regular events.

8.3.7 Disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs

Not Applicable.

8.3.8 Adverse event of special interest

Adverse event of special interest

An AESI is an AE (serious or non-serious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added, modified or removed during a study by a protocol amendment.

- Pregnancy of a female participant entered in a study as well as pregnancy occurring in a female partner of a male participant entered in a study with IMP.
  - Pregnancy occurring in a female participant entered in the clinical trial or in a female partner of a male participant entered in the clinical trial. It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Section 10.3).
  - In the event of pregnancy in a female participant, IMP should be discontinued.
  - Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined (See Section 8.3.5).
- Grade ≥3 keratopathy.
- Bundle branch blocks or any conduction defects.
- Grade ≥3 liver enzyme increased (symptomatic or asymptomatic).
- Symptomatic overdose (serious or non-serious) with IMP.
  - An overdose (accidental or intentional) with the IMP is an event suspected by the Investigator or spontaneously notified by the participant (not based on systematic pills count) and defined as an increase of at least 30% of the dose to be administered in the specified duration or if the dose is administered in less than half the recommended duration of administration.
- Dose-limiting toxicity as defined in Section 6.5.1.

8.3.9 Guidelines for reporting product complaints

Any defect in the IMP must be reported as soon as possible by the Investigator to the monitoring team that will complete a product complaint form within required timelines.

Appropriate information (eg, samples, labels or documents like pictures or photocopies) related to product identification and to the potential deficiencies may need to be gathered. The Investigator will assess whether or not the quality issue has to be reported together with an AE or SAE.

8.3.10 Guidelines for managing specific adverse events

8.3.10.1 Hypersensitivity reactions

Premedication treatments provided for treatment of hypersensitivity reactions are detailed in Section 6.1.

8.3.10.2 Ocular toxicity

It is recommended that topical artificial tears (and/or hyaluronic ophthalmic gel) are used regularly in all participants treated with tusamitamab ravtansine during the study treatment period.

The participant should be asked about ocular/visual symptoms at each visit, and ocular evaluation including visual acuity, slit-lamp examination under dilatation, and Schirmer's test should be carried out according to the SoA (Section 1.3). If ocular symptoms are present before IMP infusion, then a formal ocular examination should be performed. In participants with any ocular/visual symptom(s) (eg, blurred vision, photophobia, etc), the ocular evaluation should be repeated once weekly unless less frequent assessment is recommended by the ophthalmologist based on lesion characteristics, until resolution to Grade 1. Photographs of the cornea are recommended to be taken at the site, if possible, when ocular findings are first documented and to follow progression when relevant. Tonometry and additional ocular assessment can be performed at the discretion of the ophthalmologist when applicable.

8.3.10.2.1 Keratopathy/keratitis management

Reversible non-inflammatory, microcystic keratopathy was identified as the DLT during the dose-escalation phase in the TED13751 study with tusamitamab ravtansine. At slit-lamp examination, it presents as lesions consisting of 100s to 1000s microcysts and/or deposits that are initially observed at the periphery of the cornea, the limbus being preserved. The lesions have a centripetal distribution and evolve towards the center of the corneal upon resolution, following the natural keratinocyte regeneration process.

For standardization of AE verbatim, keratopathy should be a PT unless otherwise specified by the ophthalmologist due to inflammatory findings on eye exams leading to the diagnosis of keratitis.

The potential ocular/visual toxicity symptoms could include, but are not limited to, blurred vision, dry eye, and photophobia. Curative treatment may be used as recommended by an ophthalmologist.

No primary prophylaxis is recommended but prevention of dry eye with artificial tears and avoidance of using contact lenses should be ensured during the treatment period. Corticosteroid-containing ocular drugs are recommended in case ocular symptoms occur for the management of keratopathy/keratitis; treatment will be performed at the discretion of the ophthalmologist. Dose modification and recommendations are further described in Table 15.

Grade ≥3 keratopathy should be reported as AESI.

8.3.10.3 Management of anemia

Participants should not start Cycle 1 of treatment if hemoglobin levels are <9.0 mg/dL. Red blood cell transfusion is allowed during the screening window, but a 2-week washout period should be applied. During the treatment, erythrocyte transfusion can be given, upon Investigator decision. Erythropoietin can be given at the discretion of the Investigator, except during screening and Cycle 1. Current clinical practice should be followed for the management of anemia.

8.3.10.4 Management of neutropenia

In participants who experienced either febrile neutropenia or neutrophil count <1000 cells/mm^3 for more than one week during study intervention, prophylactic G-CSF should be implemented to ensure dose intensity and the dose should be reduced in case of recurrent events even after prophylactic G-CSF use.

If the participant continues to experience these reactions at a lower dose, treatment should be discontinued as described in Section 7.1.1.

Dose modification and discontinuation recommendations are further described in Appendix 6 (Section 10.6).

8.3.10.5 Liver function tests

Hepatic enzyme increase has been reported with tusamitamab ravtansine monotherapy. Participants should be carefully followed and in the event of Grade ≥3 abnormal liver function tests, additional liver function tests will be done every 2 to 3 days until recovery to the baseline value. Tusamitamab ravtansine should be permanently discontinued in the event of drug-induced Grade 4 liver enzyme increase.

Grade ≥3 liver enzymes increase events should be reported as AESIs.

Drug-induced liver injury, including liver failure and death, has been reported in patients receiving gemcitabine alone or with other potentially hepatotoxic drugs. Administration of gemcitabine in patients with concurrent liver metastases or a pre-existing medical history of hepatitis, alcoholism, or liver cirrhosis can lead to exacerbation of the underlying hepatic insufficiency. Assess hepatic function prior to initiation of gemcitabine and periodically during treatment. Permanently discontinue gemcitabine in patients who develop severe hepatic toxicity.

8.3.10.6 Peripheral neuropathy

Participants with a known history of peripheral neuropathies and/or patients having received medications known to cause peripheral neuropathies (eg, prior antitubulin, platinum and/or taxanes) are at high risk of developing neuropathy. Peripheral neuropathies potentially present as signs and symptoms of sensory (paresthesia, dysesthesias, pain, and change in proprioception), motor (weakness), and neural dysfunctions. There is no further recommendation beyond routine guidance on prevention and treatment of peripheral neuropathy. Cycle delays or modifications should be compliant with Section 10.6.

8.3.10.7 Colitis (including hemorrhagic)

In study TED13751 evaluating tusamitamab ravtansine in patients with several cancer types, a limited number of participants developed colitis. Based on clinical observations, patients with known underlying colitis or gastrointestinal tract conditions are noted to be at highest risk for such events. Cycle delays or modifications for symptoms of colitis should be compliant with Section 6.5.

8.3.10.8 Management of thrombocytopenia

Gemcitabine can suppress bone marrow function as manifested by leukopenia, thrombocytopenia, and anemia, and myelosuppression is usually the DLT. Patients should be monitored for platelets during therapy.

Dose modification and discontinuation recommendations are further described in Appendix 6 (Section 10.6).

8.3.10.9 Pulmonary toxicity and respiratory failure

Pulmonary toxicity, including interstitial pneumonitis, pulmonary fibrosis, pulmonary edema, and adult respiratory distress syndrome (ARDS), has been reported with gemcitabine. In some cases, these pulmonary events can lead to fatal respiratory failure despite the discontinuation of therapy. The onset of pulmonary symptoms may occur up to 2 weeks after the last dose of gemcitabine.

Permanently discontinue gemcitabine in patients who develop unexplained dyspnea, with or without bronchospasm, or evidence of severe pulmonary toxicity.

8.3.10.10 Hemolytic uremic syndrome

Hemolytic uremic syndrome (HUS), including fatalities from renal failure or the requirement for dialysis, can occur with gemcitabine. In clinical trials, HUS occurred in 0.25% of 2429 patients. Most fatal cases of renal failure were due to HUS. Serious cases of thrombotic microangiopathy other than HUS have been reported with gemcitabine.

Assess renal function prior to initiation of gemcitabine and periodically during treatment. Consider the diagnosis of HUS in patients who develop anemia with evidence of microangiopathic hemolysis; increased bilirubin or LDH; reticulocytosis; severe thrombocytopenia; or renal failure (increased serum creatinine or BUN). Permanently discontinue gemcitabine in patients with HUS or severe renal impairment. Renal failure may not be reversible even with the discontinuation of therapy.

8.3.10.11 Capillary leak syndrome

Capillary leak syndrome (CLS) with severe consequences has been reported in patients receiving gemcitabine as a single agent or in combination with other chemotherapeutic agents. Permanently discontinue gemcitabine if CLS develops during therapy.

8.3.10.12 Posterior reversible encephalopathy syndrome

Posterior reversible encephalopathy syndrome (PRES) has been reported in patients receiving gemcitabine as a single agent or in combination with other chemotherapeutic agents. PRES can present with headache, seizure, lethargy, hypertension, confusion, blindness, and other visual and neurologic disturbances. Confirm the diagnosis of PRES with magnetic resonance imaging (MRI). Permanently discontinue gemcitabine if PRES develops during therapy.

8.4 PHARMACOKINETICS

Blood samples will be collected for the measurement of tusamitamab ravtansine (SAR408701), gemcitabine and its metabolite (dFdU) concentrations as described in the PK/ATA flowcharts (Section 1.3.3). The actual date and time of each sample will be recorded. Instructions for the collection and handling of PK samples will be provided by the Sponsor's designee in a separate laboratory manual. These samples will be tested by the Sponsor or Sponsor's designee.

Pharmacokinetic samples could be used for testing analytical method performance such as comparability and incurred sample reproducibility and for possible exploratory analysis of drug metabolites. The exploratory data will not be included in the study report but will be kept on file.

8.4.1 Noncompartmental analysis

Pharmacokinetic parameters of SAR408701, gemcitabine, and dFdU will be calculated using noncompartmental methods from concentrations obtained after administration assayed in the first 10 participants. The parameters will include, but may not be limited to, those listed in Table 9.

Table 9 - List of pharmacokinetic parameters and definitions

Analyte	Cycle/Day	Parameter	Definition
tusamitamab ravtansine	1/1	C_{max}	Maximum concentration observed after infusion
		$AUC_{0\text{-}14d}$	Area under the plasma concentration versus time curve calculated using the trapezoidal method from time 0 to 14 days.
gemcitabine	1/1	CL	Total body clearance of a drug from plasma calculated using the following equation from AUC: CL=dose/AUC
dFdU	1/1	C_{max}	Maximum concentration observed after infusion

8.4.2 Population approach

Data from plasma concentrations of tusamitamab ravtansine may be used for population PK analysis by nonlinear, mixed-effects modeling. Empirical Bayesian estimation of individual exposure parameters such as maximum concentration (C_{max}), trough concentration (C_{trough}), and area under the curve (AUC) will be derived. The population PK analysis will be reported in a standalone report (s).

8.5 GENETICS

8.5.1 Circulating tumor DNA analysis

A 20 mL blood sample corresponding to about 10 mL of plasma for tumor circulating free deoxyribonucleic acid (cfDNA) isolation and an additional 2 mL blood sample for germline DNA will be collected at pre-infusion of Cycle 1 Day 1.

Samples are planned to be transferred to a central laboratory for cfDNA/DNA extraction and mutational profiling of key cancer genes to understand the significance of existing mutation during tusamitamab ravtansine treatment.

Fragmented circulating tumor DNA or cfDNA is released from the tumor in the plasma and can readily be extracted and analyzed for mutation of common cancer genes. Subtractive mutation analysis will be performed with germline DNA data to identify tumor specific somatic genetic aberrations. Mutation profiling analysis will be performed and the potential correlation of specific mutation(s) with clinical outcomes will be assessed.

The list (not exhaustive) of the genes that could be mutated is: AKT1, ALK, BRAF, CDKN1B, CDKN2A, CDKN2D, EGFR, ESR1, FGFR4, HER2, HRAS, KRAS, MDM2, MED1, MET, NRAS, PIK3CA, PTEN, RB1, RET, ROS1, and TP53.

8.5.2 Tumor DNA and RNA analyses

Although tumor CEACAM5 expression is a major parameter driving the activity of an anti-CEACAM5 ADC such as tusamitamab ravtansine, other factors may significantly contribute. Tumor tissue will therefore also be requested to explore the potential relationship between clinical endpoints following tusamitamab ravtansine therapy and potential sets of biomarkers besides target expression that could be predictive of response.

For that purpose, 3 × 10 µm slides (or equivalent such as 6 × 5 µm or other) from the same sample as the one sent for CEACAM5 assessment at prescreening are requested at screening or Cycle 1 Day 1. The samples may serve to investigate other potential biomarkers of response. In tumor tissue, biomarker annotation could include, but may not be restricted to, genomic annotation by sequencing, gene copy number variation, gene expression (mRNA and miRNA), and proteomic profiling.

See Appendix 5 (Section 10.5) for information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in the study laboratory manual.

8.6 BIOMARKERS

Samples collected for biomarker analyses and their derivatives will be stored for a period of up to 15 years after last participant last visit for potential re-analyses.

8.6.1 Pharmacodynamics

Circulating carcinoembryonic antigen (CEA) levels will be collected at prescreening, baseline, during the treatment (every 8 weeks), EOT, and follow-up period (every 12 weeks) at the time of laboratory assessment as close as possible to tumor assessment (and no more than 2 weeks from the tumor assessment) until confirmed disease progression. It will be assessed using local testing.

Venous blood samples of approximately 3 mL (volume may change depending on local laboratory assay) will be collected for measurement at the local laboratory.

8.6.2 Other biomarkers

- Collection of samples for other biomarker research is also part of this study. The following samples for biomarker research are required and will be collected from all participants in this study as specified in the SoA:
  - Tumor tissue samples will be collected and assayed for CEACAM5 expression to determine eligibility for this study. For mBC, a tissue sample collected at the metastatic site is mandatory. For mPAC, a tissue sample collected at the metastatic site is preferable but primary tumor samples are also accepted.
  - Additionally, for mBC and if available, 3 × 5-µm slides from the surgery material at the breast cancer diagnosis (primary tumor or local lymph nodes) are requested for CEACAM5 assessment.
  - Blood sample will be collected for CTC detection to assess the expression of CEACAM5 on these cells (optional for Cohort A and Cohort B).
  - Blood sample will be collected for IgG dosage to explore impact of IgG level on PK of tusamitamab ravtansine (only for Cohort C).
- Instructions for the collection and handling of biological samples will be provided by the Sponsor in a separate laboratory manual.
- The level of CEACAM5 expression in tumor tissues will be determined by a central laboratory using a specific anti-CEACAM5 antibody (clone 769).

Assessment of CTC at pre-infusion of Cycle 1 Day 1 will be determined by a central laboratory. For this test, 10 mL of blood will be collected. Samples will be taken from approximately 5 participants per Cohort (Cohorts A and Cohort B).

8.7 IMMUNOGENICITY ASSESSMENTS

Blood samples will be collected for assessing the presence of ATA against tusamitamab ravtansine in plasma from all participants as described in SoA (Section 1.3). These samples will be tested by the Sponsor's designee. The remaining plasma volume may also be used for further investigations (including pharmacokinetic assessment) if deemed relevant.

Refer to the laboratory manual for details regarding sample collection, processing, storage, and shipment.

Plasma samples will be screened for antibodies binding to tusamitamab ravtansine and the titer of confirmed positive samples will be reported.

8.8 HEALTH ECONOMICS

No health economics data will be collected.

8.9 USE OF BIOLOGICAL SAMPLES AND DATA FOR FUTURE RESEARCH

Future research may help further the understanding of disease subtypes, disease biology, related conditions, mechanism of action, or possible toxicity, and can help identify new drug targets or biomarkers that predict participant response to treatment. Therefore, data and biological samples will be stored and used for future research when consented to by participants (see Section 10.1.3) unless prohibited by local laws or IRBs/IECs (in such case, consent for future use of sample will not be included in the local ICF).

For participants who consent to the storage and use of their data and remaining (leftover) and/or extra (additional) clinical samples, data and samples may be used for future research related either to the drug, the mechanism of action, and the disease or its associated conditions. Such research may include, but is not limited to, performing assessments on DNA, RNA, proteins or metabolites. If future research on genetic material is performed, this will also be limited to the purpose of addressing research questions related to the drug, the mechanism of action, the disease or its associated conditions.

Remaining leftover samples will be used only after the study ends, ie end of study as defined in the study protocol. Additional/extra samples can be collected and used during the study conduct at a given timepoint (eg, at randomization visit) as defined in the study protocol.

In the event future research is conducted for other purposes, the study participants will be informed of those purposes and will be given means to object to those research projects.

Data and samples will be used in alignment with the information provided to participants in the ICF Part 2 (future research).

For future research projects, all biological samples and relating data to be used will be coded such that no participant direct identifiers will be linked to them. These coded data and samples may be transferred to a Sponsor site (or a subcontractor site), which may be located outside of the country where the study is conducted. The Sponsor adopts safeguards for protecting participant confidentiality and personal data (see Section 10.1.4).

Relating data and biological samples for future research will be stored for up to 25 years after the end of the study. Any samples remaining at the end of retention period will be destroyed. If a participant requests destruction of his/her samples before the end of the retention period, the Investigator must notify the Sponsor (or its contract organization) in writing. In such case, samples will be destroyed and related coded data will be anonymized unless otherwise required by applicable laws.

Participant's coded datasets provided to researchers for a specific research project will be available to the researchers for a maximum of 2 years after the end of their specific project (end of project is defined by publication of the results or finalization of the future research project report).

9 STATISTICAL CONSIDERATIONS

The statistical analysis plan will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.1 SAMPLE SIZE DETERMINATION

Assuming a prescreening failure rate of 90% for the mBC Cohort A, 85% for mPAC Cohort B, and 58% for mPAC Cohort C, and a screening failure rate of 20% for the 3 cohorts, approximately 440 participants for the mBC Cohort A, 242 participants for the mPAC Cohort B, and 90 participants for mPAC Cohort C will be prescreened to achieve up to approximately 35 treated participants evaluable for activity (at least 1 postbaseline tumor assessment, early progression, or death due to progressive disease) for the mBC Cohort A, 29 treated participants evaluable for activity for mPAC Cohort B, and 30 participants evaluable for activity in mPAC Cohort C.

For Cohort C safety run-in (Part 1), the actual sample size is expected to vary depending on DLTs observed. It is anticipated that around 3 to 12 DLT-evaluable participants will be enrolled. Table 10 and Table 11 list the estimated ORRs and 95% exact CIs by the numbers of responders from a sample size of 35 treated participants evaluable for activity for the mBC cohort, 29 treated participants evaluable for activity for mPAC cohort, and Table 12 lists the estimated ORRs and CIs 30 treated participants evaluable for activity for combination cohort.

Table 10 - [redacted]

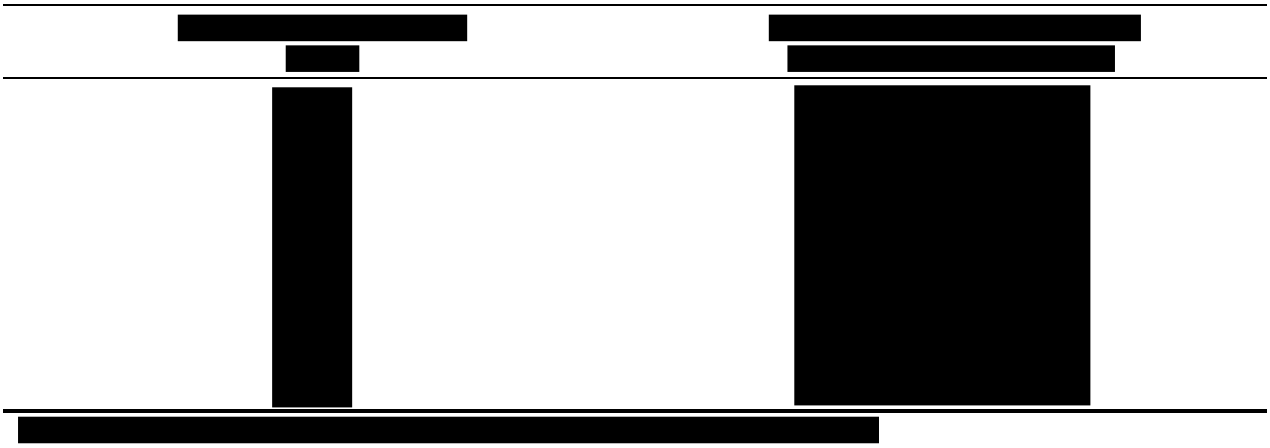


Table 11 - [redacted]

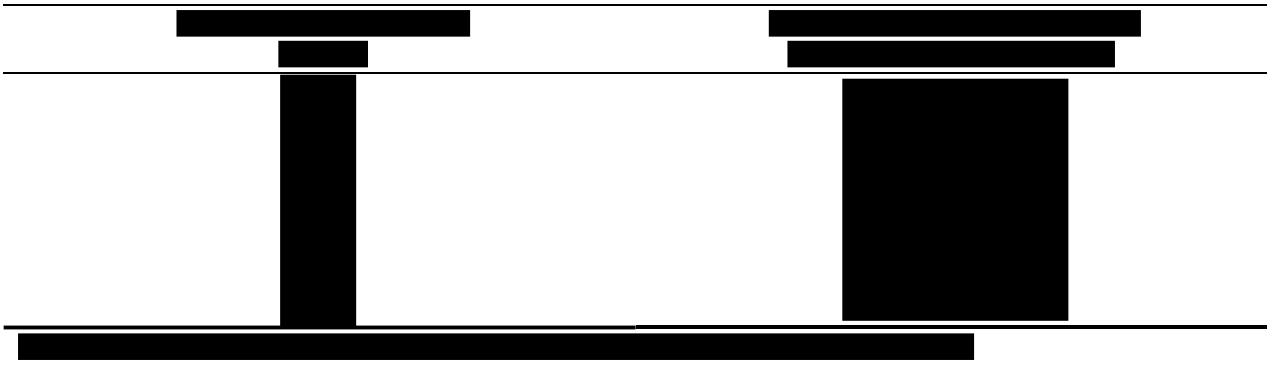
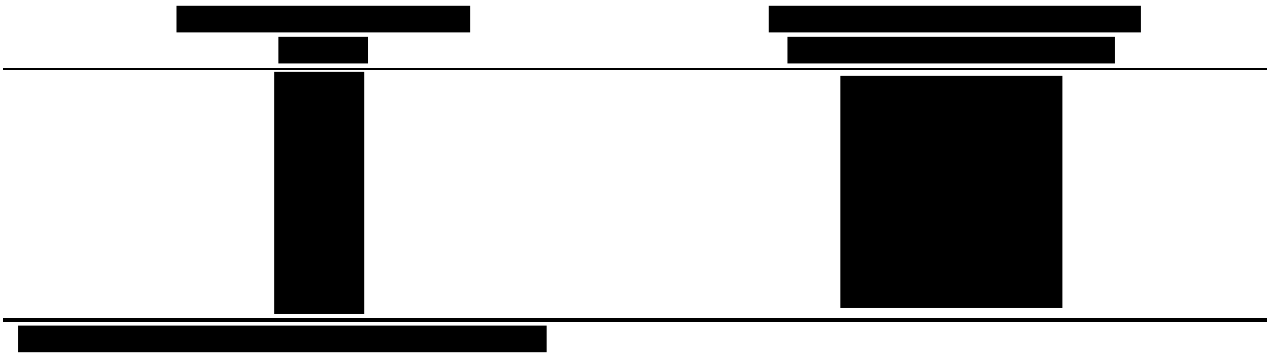


Table 12 - [redacted]



9.2 POPULATIONS FOR ANALYSES

The following populations are defined in Table 13:

Table 13 - Populations for analyses

Population	Description
Prescreened	All participants who signed the prescreening informed consent for CEACAM5 assay assessment of their biopsy.
Screened	All participants who signed screening informed consent for study participation.
DLT-Evaluable (Cohort C Part 1)	Participants who received 1 cycle with at least 80% of the intended dose for tusamitamab ravtansine at each of the first 2 infusions and gemcitabine at each of the first 3 infusions unless they discontinued the study intervention before the end of Cycle 1 due to a DLT.
All-treated	All registered participants exposed to the study treatment, regardless of the amount of treatment administered. This population is the primary population for all efficacy parameters.
Activity	All treated participants who have measurable disease at study entry and at least one post-baseline evaluable tumor assessment. Participants with no post-baseline evaluable tumor assessment but with an early clinical progression or who died from disease progression will also be included in this set. This population is the secondary population for analysis of efficacy parameters.

PK	All treated participants with at least 1 postbaseline PK result with adequate documentation of dosing and sampling dates and times.
ATA	All treated participants with at least one post-baseline ATA result (negative, positive, or inconclusive).

CEACAM5 = carcinoembryonic antigen-related cell adhesion molecule 5; ATA = antittherapeutic antibodies.

Participants exposed to study intervention before or without being enrolled will not be considered enrolled and will not be included in any analysis population. The safety experience of these participants will be reported separately.

Enrolled participants for whom it is unclear whether they took the study intervention will be considered as exposed and will be included in the safety population.

For any participant enrolled more than once, only the data associated with the first enrollment will be used in any analysis population. The safety experience associated with any later enrollment will be reported separately.

9.3 STATISTICAL ANALYSES

The statistical analysis plan will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.3.1 General considerations

This study is designed to obtain preliminary efficacy and safety data on the use of tusamitamab ravtansine administered to participants with CEACAM5-positive tumors known to be sensitive to anti-tubulin agents at a loading dose of 170 mg/m² on Day 1 of Cycle 1, followed by 100 mg/m² Q2W for Cohorts A and B, and at a loading dose of 170 mg/m² (or 135 mg/m²) on Day 1 of Cycle 1, followed by 100 mg/m² Q2W, combined with gemcitabine 1000 mg/m² on Day 1, Day 8, and Day 15 every 4 weeks (Q4W), for Cohort C.

As this study is not intended to explicitly test a hypothesis, calculations of power and Type I error were not considered in the study design; 95% CIs will be provided for the primary and secondary efficacy endpoints. Each cohort will be analyzed separately.

All efficacy analyses will be performed on the All-treated population (primary population for all efficacy parameters). In addition, the primary endpoint (ORR as per RECIST v1.1) and DCR will be analyzed on the activity population (secondary population). Objective response rate, as well as PFS, DCR and DOR, will be derived using the local radiologist's/Investigator's assessment.

The study cut-off for the primary analysis (ORR) for each cohort corresponds to the date on which all treated evaluable participants of the cohort have had at least 2 postbaseline tumor assessments, experienced confirmed objective response, or have discontinued the study for any reason. For participants with 2 postbaseline tumor assessments and occurrence of response at the second

post-baseline tumor assessment, it will also include the confirmatory assessment. An interim analysis will be performed when the first 15 treated evaluable participants in Cohort C have had at least 2 postbaseline tumor assessments, experienced confirmed objective response, or have discontinued the study for any reason. Once 15 participants have been treated, enrollment may be paused until a decision regarding the interim analysis can be made.

The analysis cut-off date for secondary efficacy endpoints including DOR and PFS (final cut-off date) will be 6 months after the cut-off date of the primary analysis. The primary analysis of ORR and DCR will also be updated at that time.

All safety analyses will be performed on the All-treated population. Summaries of safety data will be provided by participant. For each safety parameter, the baseline value will be defined as the latest value or measurement taken before the first administration of the IMP.

The observation period will be divided into 4 segments:

- The prescreening period is defined as the time from when the participants give prescreening informed consent to the day before the screening informed consent.
- The screening period is defined as the time from when the participants give screening informed consent to the first administration of the IMP.
- The treatment period is defined as the time from the first administration of IMP up to 30 days after the last administration of IMP.
- The post-treatment period is defined as the time from the 31st day after the last administration of IMP to study closure or death, whichever occurs first.

9.3.2 Primary endpoint(s)

The primary efficacy endpoint is the ORR. The ORR will be estimated by dividing the number of participants with confirmed objective response (CR or PR as best overall response [BOR]), determined according to RECIST v1.1, by the number of participants from the analysis population.

The BOR is the best tumor response observed from the date of first IMP administration until disease progression, death, cut-off date or initiation of post-treatment anti-cancer therapy, whichever occurs first.

ORR will be summarized for the All-treated population with descriptive statistics. In addition, 2-sided 95% CIs will be computed using the Clopper-Pearson method.

ORR will also be summarized on the activity population as a supplementary analysis.

A primary endpoint for Part 1 of Cohort C is DLTs observed during the 28 day DLT observation period (Cycle 1); incidences of DLTs will be summarized on the DLT-evaluable population, by dose level. In addition, AEs that meet the DLT criteria in subsequent cycles will be summarized on the all-treated population. Details will be provided by participant.

9.3.3 Secondary endpoint(s)

The safety and efficacy secondary endpoints include safety, PFS, DCR, DOR per RECIST v1.1, PK and immunogenicity.

9.3.3.1 Adverse events

Adverse events will be collected from the time prescreening informed consent is signed until at least 30 days after the last infusion of the study treatment. All AEs will be categorized according to NCI-CTCAE v5.0 and classified by SOC and PT according to the latest available version of the medical dictionary for regulatory activities (MedDRA).

- Prescreening AEs are defined as AEs occurring during the prescreening period.
- Screening AEs are defined as any AEs occurring during the screening period.
- Treatment-emergent AEs are defined as AEs that develop, worsen (according to the Investigator's opinion), or become serious during the treatment period.
- Post-treatment AEs are defined as AEs that are reported during the post-treatment period.

The NCI-CTCAE grade will be taken into account in the summary of AEs. For participants with multiple occurrences of the same PT, the maximum grade will be used.

The primary focus of AE reporting will be on TEAEs. Prescreening, screening, and post-treatment AEs will be described separately.

Treatment-emergent adverse events:

An overall summary of TEAEs will be provided. The number and percentage of participants experiencing any of the following will be provided:

- TEAEs
- Grade ≥3 TEAEs
- Grade 5 TEAEs (any TEAE with a fatal outcome during the treatment period)
- Serious TEAEs
- TEAEs leading to definitive treatment discontinuation
- Treatment-related TEAEs
- Treatment-related Grade ≥3 TEAEs
- Serious treatment-related TEAEs
- AESI

The number and percentage of participants experiencing TEAEs by primary SOC and PT will be summarized by NCI-CTCAE v5.0 grade (all grades and Grade ≥3) for the All-treated population. Similar summaries will be prepared for treatment-related TEAEs, TEAEs leading to definitive

discontinuation, TEAEs leading to dose modification, serious TEAEs, TEAEs with fatal outcome, AESIs, and AEs/SAEs occurring during the post-treatment period. In addition, the number and percentage of participants with any Grade 5 AE (TEAE and post-treatment) will be summarized.

9.3.3.2 Deaths

The following deaths summaries will be generated:

- Number and percentage of participants who died by study period (treatment, post-treatment) and reasons for death (disease progression, AE, or other reason).
- Deaths in registered but not treated participants.
- All TEAEs leading to death by primary SOC and PT showing the number and percentage of participants.

9.3.3.3 Clinical laboratory evaluations

Clinical laboratory values will be analyzed after conversion into standard international units. International units will be used in all listings and tables.

Hematology and clinical chemistry results will be graded according to the NCI-CTCAE v5.0, when applicable. The number and percentage of participants with laboratory abnormalities (all grades and by grade) using the worst grade during the treatment period will be summarized for the All-treated population.

When the NCI-CTCAE v5.0 grading scale is not applicable, the number of participants with a laboratory abnormality out-of-normal range value will be displayed.

9.3.3.4 Progression-free survival

Progression-free survival is defined as the time from the date of first IMP administration to the date of the first radiological documentation of progressive disease according to RECIST v1.1 or death due to any cause before the analysis cut-off date, whichever occurs first.

The analysis of PFS will be based on the following censoring rules:

- If progression or death is not observed before the cut-off date and prior to the initiation of a further anti-cancer therapy, then PFS will be censored at the date of the last valid tumor assessment performed before the analysis cut-off date or date of initiation of a further anti-cancer therapy, whichever is earlier.
- A participant without an event (death or disease progression) and without any valid post-baseline tumor assessment will be censored at the day of first IMP administration (Day 1).

Progression-free survival will be summarized on the All-treated population using Kaplan-Meier methods. The median PFS time and associated 95% CI will be provided along with probabilities of being progression-free at different time points.

9.3.3.5 Disease control rate

The DCR will be estimated by dividing the number of participants with confirmed objective response or stable disease (CR or PR or stable disease as BOR), determined according to RECIST v1.1, by the number of participants from the analysis population.

The DCR will be summarized for the All-treated population with descriptive statistics. In addition, 2-sided 95% CIs will be computed using the Clopper-Pearson method.

Disease control rate will also be summarized on the activity population as a supplementary analysis.

9.3.3.6 Duration of response

The DOR will be defined as the time from the date of first initial occurrence of the confirmed CR or PR to the date of first radiological documentation of progressive disease according to RECIST v1.1 before the initiation of any post-treatment anti-cancer therapy or death due to any cause, whichever occurs first.

In the absence of disease progression or death before the cut-off date, DOR will be censored at the date of the last valid tumor assessment performed before the analysis cut-off date or date of initiation of new anti-cancer therapy, whichever is earlier. Duration of response will be summarized with descriptive statistics using Kaplan-Meier methods. The median DOR and associated 95% CI will be provided.

The DOR will only be summarized on the subgroup of participants who have achieved confirmed objective response in the All-treated population.

9.3.3.7 Immunogenicity

Immunogenicity analyses and the potential impact on safety and efficacy will be described in the statistical analysis plan (SAP); analyses will be performed on the ATA population.

9.3.3.8 Pharmacokinetics

Pharmacokinetic analyses are described briefly in Section 8.4.1, and will be described in the statistical analysis plan.

The population PK methodology is described briefly in Section 8.4.2, and will be described in a separate report provided by the Pharmacokinetics, Dynamics, and Metabolism (PKDM) Modeling and Simulation group.

9.3.4 Tertiary/exploratory endpoint(s)

Biomarker analyses will be described in the SAP.

9.3.5 Other analyses

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 9 (Section 10.9).

9.4 INTERIM ANALYSES

An interim analysis based on the number of responses observed in the Activity population for the cohort of patients with metastatic pancreatic cancer will be performed.

The cut-off date for the interim analysis corresponds to the date when the first 15 treated evaluable participants in Cohort C who have had at least 2 postbaseline tumor assessments or experienced confirmed objective response, or have discontinued the study for any reason. For participants with 2 postbaseline tumor assessments and occurrence of response at the second postbaseline tumor assessment, the confirmatory assessment will also be included. Approximately up to 20 participants may be enrolled to reach the 15 treated evaluable participants, if needed.

For Cohort C, if 1 or 0 confirmed response is observed among the first 15 treated participants evaluable for activity, the cohort will be closed.

The statistical analysis plan will describe the planned interim analyses in greater detail.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 APPENDIX 1: REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and the applicable amendments and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
  - Applicable ICH GCP Guidelines.
  - Applicable laws and regulations (eg, data protection law as General Data Protection Regulation [GDPR]).
- The protocol, protocol amendments, ICF, IB, [IDFU] and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Determining whether an incidental finding (as per Sanofi policy) should be returned to a participant and, if it meets the appropriate criteria, to ensure the finding is returned (an incidental finding is a previously undiagnosed medical condition that is discovered unintentionally and is unrelated to the aims of the study for which the tests are being performed). The following should be considered when determining the return of an incidental finding:
    - The return of such information to the study participant (and/or his/her designated healthcare professional, if so designated by the participant) is consistent with all applicable national, state, or regional laws and regulations in the country where the study is being conducted, and
    - The finding reveals a substantial risk of a serious health condition or has reproductive importance, AND has analytical validity, AND has clinical validity.

- The participant in a clinical study has the right to opt out of being notified by the Investigator of such incidental findings. In the event that the participant has opted out of being notified and the finding has consequences for other individuals, eg, the finding relates to a communicable disease, Investigators should seek independent ethical advice before determining next steps.
- In case the participant has decided to opt out, the Investigator must record in the site medical files that she/he does not want to know about such findings.

- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

As applicable, according to Directive 2001/20/EC, the Sponsor will be responsible for obtaining approval from the Competent Authorities of the EU Member States and/or Ethics Committees, as appropriate, for any amendments to the clinical trial that are deemed as "substantial" (ie, changes which are likely to have a significant impact on the safety or physical or mental integrity of the clinical trial participants or on the scientific value of the trial) prior to their implementation.

10.1.2 Financial disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed consent process

- The Investigator or his/her representative will explain the nature of the study to the participants, and answer all questions regarding the study, including what happens to the participant when his/her participation ends (post-trial access strategy for the study).
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Privacy and Data Protection requirements including those of the GDPR and of the French law, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- In case of ICF amendment while the participants are still included in the study, they must be re-consented to the most current version of the ICF(s). Where participants are not in the

study anymore, teams in charge of the amendment must define if those participants must or not re-consent or be informed of the amendment (eg, if the processing of personal data is modified, if the Sponsor changes, etc).

- A copy of the ICF(s) must be provided to the participant, where applicable.

The ICF contains 2 separate sections that addresses the use for research of participants' data and/or samples (remaining mandatory ones or new extra samples collected for optional research). Optional exploratory research must be detailed in the section "Optional tests/procedures" and future research is to be defined in Core Study Informed Consent Form (CSICF) Part 2. Each option is subject to an independent consent and must be confirmed by ticking a checkbox in CSICF Part 3. The Investigator or authorized designee will explain to each participant the objectives of the exploratory research and why data and samples are important for future research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 9 (Section 10.9).

10.1.4 Data protection

All personal data collected and/or processed in relation to this study will be handled in compliance with all applicable Privacy and Data Protection laws and regulations, including the GDPR. The study Sponsor is the Sanofi company responsible for ensuring compliance with this matter, when processing data from any individual who may be included in the Sanofi databases, including Investigators, nurses, experts, service providers, Ethics Committee members, etc.

When archiving or processing personal data pertaining to the Investigator and/or to the participants, the Sponsor takes all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

Protection of participant data

Data collected must be adequate, relevant and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objective.

Participant race and ethnicity will be collected in this study because they are expected to modify the drug response/because they are required by regulatory agencies (eg, on African American population for the FDA or on Japanese population for the Pharmaceuticals and Medical Devices Agency in Japan). They will not be collected in the countries where this is prohibited by local regulation.

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor or its service providers will be identifiable only by the unique identifier; participant names or any information which would make the participant identifiable will not be transferred to the Sponsor.

- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with applicable data protection laws. The level of disclosure must also be explained to the participant as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- Participants must be informed that their study-related data will be used for the whole "drug development program", ie, for this trial as well as for the following steps necessary for the development of the investigational product, including to support negotiations with payers and publication of results.

Protection of data related to professionals involved in the study

- Personal data (eg, contact details, affiliation(s) details, job title and related professional information, role in the study, professional resume, training records) are necessary to allow Sanofi to manage involvement in the study and/or the related contractual or pre-contractual relationship. They may be communicated to any company of the Sanofi group ("Sanofi") or to Sanofi service providers, where needed.
- Personal data can be processed for other studies and projects. At any time, objection to processing can be made by contacting the Sanofi Data Protection Officer (link available at Sanofi.com).
- In case of refusal to the processing of personal data by or on behalf of Sanofi, it will be impossible to involve the professionals in any Sanofi study. In case the professionals have already been involved in a Sanofi study, they will not be able to object to the processing of their personal data as long as they are required to be processed by applicable regulations. The same rule applies in case the professionals are listed on a regulatory agencies disqualification list.
- Personal data can be communicated to the following recipients:
  - Personnel within Sanofi or partners or service providers involved in the study.
  - Judicial, administrative and regulatory authorities, in order to comply with legal or regulatory requirements and/or to respond to specific requests or orders in the framework of judicial or administrative procedures. Contact details and identity may also be published on public websites in the interest of scientific research transparency.
- Personal data may be transferred towards entities located outside the Economic European Area, in countries where the legislation does not necessarily offer the same level of data protection or in countries not recognized by the European Commission as offering an adequate level of protection. Those transfers are safeguarded by Sanofi in accordance with the requirement of European law including, notably:
  - The standard contractual clauses of the European Commission for transfers towards our partners and service providers,
  - Sanofi's Binding Corporate Rules for intra-group transfers.

- Professionals have the possibility to lodge a complaint with Sanofi leading Supervisory Authority, the "Commission Nationale de l'Informatique et des Libertés" (CNIL) or with any competent local regulatory authority.
- Personal data of professionals will be retained by Sanofi for up to thirty (30) years, unless further retention is required by applicable regulations.
- In order to facilitate the maintenance of Investigators personal data, especially if they contribute to studies sponsored by several pharmaceuticals companies, Sanofi participates in the Shared Investigator Platform (SIP) and in the TransCelerate Investigator Registry (IR) project (https://transceleratebiopharmainc.com/initiatives/investigator-registry/). Therefore, personal data will be securely shared by Sanofi with other pharmaceutical company members of the TransCelerate project. This sharing allows Investigators to keep their data up-to-date once for all across pharmaceutical companies participating in the project, with the right to object to the transfer of the data to the TransCelerate project.
- Professionals have the right to request the access to and the rectification of their personal data, as well as their erasure (where applicable) by contacting the Sanofi Data Protection Officer: Sanofi DPO - 54 rue La Boétie - 75008 PARIS - France (to contact Sanofi by e-mail, visit https://www.sanofi.com/en/our-responsibility/sanofi-global-privacy-policy/contact).

10.1.5 Committees structure

The SC includes the Investigators or designees and Sponsor team members and, when appropriate, ad hoc experts. Decisions to continue the enrollment at a DL or to reduce the dose to be tested will be made after the appropriate data are collected and reviewed by the SC. The SC will convene regularly (eg, every 2 weeks) during Part 1 of Cohort C; and may meet ad hoc for specific discussions. Meeting minutes will be documented.

10.1.6 Dissemination of clinical study data

Study participants

Sanofi shares information about clinical trials and results on publicly accessible websites, based on company commitments, international and local legal and regulatory requirements, and other clinical trial disclosure commitments established by pharmaceutical industry associations. These websites include clinicaltrials.gov, EU clinicaltrialregister (eu.ctr), and sanofi.com, as well as some national registries.

In addition, results from clinical trials in patients are required to be submitted to peer-reviewed journals following internal company review for accuracy, fair balance and intellectual property. For those journals that request sharing of the analyzable data sets that are reported in the publication, interested researchers are directed to submit their request to https://vivli.org.

Individual participant data and supporting clinical documents are available for request at clinicalstudydatarequest.com. While making information available we continue to protect the

privacy of participants in our clinical trials. Details on data sharing criteria and process for requesting access can be found at this web address:https://vivli.org.

Professionals involved in the study or in the drug development program

Sanofi may publicly disclose, and communicate to relevant authorities/institutions, the funding, including payments and transfers of value, direct or indirect, made to healthcare organizations and professionals and/or any direct or indirect advantages and/or any related information or document if required by applicable law, by regulation or by a code of conduct such as the "EFPIA Code on Disclosure of Transfers of Value from Pharmaceutical Companies to Healthcare Professionals and Healthcare Organisations".

10.1.7 Data quality assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in CRF completion instructions.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in separate study documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 25 years after the signature of the final study report unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8 Source documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be

explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

- Every data point recorded in the CRF must have a source document (SD). The Investigator/delegated site staff will report all the original data in the participant's medical chart or in a study specific SD created by him/her. If such document is used, the template should be reviewed by the CRA. A list of SD and their location will be filed in the Investigator Study File.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9 Study and site start and closure

First act of recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

Study/Site termination

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for study termination by the Sponsor, as well as reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- For study termination:
  - Information on the product leads to doubt as to the benefit/risk ratio.
  - Discontinuation of further study intervention development.
- For site termination:
  - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.

- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator.
- Total number of participants included earlier than expected.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10 Publication policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multi-center studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 APPENDIX 2: CLINICAL LABORATORY TESTS

- The tests detailed in Table 14 will be performed by the local laboratory with the exception of CEACAM5 immunohistochemistry, CTC evaluation (optional), ATA, cfDNA/Germline DNA, and tumor DNA/RNA analysis, which will be performed in the central laboratory or another external laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.
- Pregnancy testing (urine or serum as required by local regulation) should be conducted in all WOCBP at Screening, then every 4 weeks from Cycle 2, and at the EOT, as detailed in the SoA (Section 1.3). Women of childbearing potential must have a negative serum pregnancy test result within 7 days prior to the initial intervention and at the EOT evaluation (30 ±5 days after the last IMP administration). Additionally, during the treatment period, serum/urine pregnancy tests will be performed at the beginning of the visit every 4 weeks.

Table 14 - Protocol-required laboratory tests

Laboratory assessments	Parameters
Hematology	
	Platelet count
	Red blood cell (RBC) count
	Hemoglobin
	Hematocrit
	White blood cell (WBC) count with differential:
	Neutrophils[a]
	Lymphocytes
	Monocytes
	Eosinophils
	Basophils
Coagulation	International normalized ration (INR)
Clinical chemistry[b]	
	Urea or Blood urea nitrogen (BUN)
	Creatinine
	Potassium
	Sodium
	Calcium
	Phosphate
	Chloride
	Aspartate aminotransferase (AST)
	Alanine aminotransferase (ALT)
	Lactate dehydrogenase (LDH)
	Glucose
	Alkaline phosphatase
	Total and direct bilirubin
	Albumin
	Total protein
	Circulating carcinoembryonic antigen (CEA)
Other screening tests	• Highly sensitive serum or urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[c] • Serology (HIV antibody, hepatitis B surface antigen [HBsAg] or hepatitis B viral DNA, and hepatitis C virus antibody or HCV RNA) if applicable as per local regulatory requirement • CEACAM5 expression status on tumor tissue • CEACAM5 expression on CTCs in blood (Cycle 1 Day 1 pre-infusion) – optional • cfDNA/Germline DNA analysis • Tumor DNA/RNA analysis • ATA All study-required laboratory assessments will be performed by a local laboratory, with the exception of CEACAM5 expression, cfDNA/Germline DNA analysis, tumor DNA/RNA analysis, and ATA. The results of each test must be entered into the CRF

NOTES:
a If Grade 4 neutropenia, assess ANC every 2 to 3 days until ANC ≥0.5 x 10^9/L.

b Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 8.3.10.5. All events of ≥ Grade 3 ALT/AST increase must be reported as an AESI. Investigators must document their review of each laboratory safety report.
c Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

Investigators must document their review of each laboratory safety report.

10.3 APPENDIX 3: AES AND SAES: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

10.3.1 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Definition of unsolicited and solicited AE

- An unsolicited adverse event is an adverse event that was not solicited using a participant diary and that is communicated by a participant who has signed the informed consent. Unsolicited AEs include serious and non-serious AEs.
- Potential unsolicited AEs may be medically attended (ie, symptoms or illnesses requiring a hospitalization, or emergency room visit, or visit to/by a health care provider). The participant will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.
- Unsolicited AEs that are not medically attended nor perceived as a concern by participant will be collected during interview with participant and by review of available medical records at the next visit.
- Solicited AEs are pre-defined local and systemic events for which the participant is specifically questioned, and which are noted by the participants in their diary.

Events <u>meeting</u> the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease), eg:
  - Leading to IMP discontinuation or modification of dosing, and/or

- Fulfilling a seriousness criterion, and/or
- Defined as an AESI

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events NOT meeting the AE definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

An SAE is defined as any adverse event that, at any dose:

a) Results in death

c) Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

d) Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

e) Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

f) Is a congenital anomaly/birth defect

g) Is a suspected transmission of any infectious agent via an authorized medicinal product

h) Other situations:

- Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
  - Note: The following list of medically important events is intended to serve as a guideline for determining which condition has to be considered as a medically important event. The list is not intended to be exhaustive:
    - Intensive treatment in an emergency room or at home for:
      - Allergic bronchospasm.
      - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc)
      - Convulsions (seizures, epilepsy, epileptic fit, absence, etc)
    - Development of drug dependence or drug abuse
    - ALT >3 × ULN + total bilirubin >2 × ULN or asymptomatic ALT increase >10 × ULN
    - Suicide attempt or any event suggestive of suicidality

- Syncope, loss of consciousness (except if documented as a consequence of blood sampling)
- Bullous cutaneous eruptions

10.3.3 Recording and follow-up of AE and/or SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor's representative in lieu of completion of the required form.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor's representative. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor's representative.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories according to NCI-CTCAE v5.0.

An event is defined as "serious" when it meets at least 1 of the pre-defined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than that a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.

- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the monitoring team.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor's representative to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE reporting to the Sponsor via an electronic data collection tool

- The primary mechanism for reporting an SAE to the Sponsor's representative will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Sponsor's representative by telephone.
- Contacts for SAE reporting can be found in the Investigator study file.

SAE reporting to the Sponsor via paper data collection tool

- Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the Sponsor's representative.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in the Investigator study file.

10.4 APPENDIX 4: CONTRACEPTIVE AND BARRIER GUIDANCE

10.4.1 Definitions

A woman is considered WOCBP (fertile) from the time of menarche until becoming postmenopausal (see below) unless permanently sterile (see below).

- A postmenopausal state is defined as the period of time after a woman has experienced no menses for 12 consecutive months without an alternative medical cause.
- A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.
- Permanent sterilization methods include:
- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy
- For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), Investigator discretion should be applied to determining study entry eligibility.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first administration of study intervention, additional evaluation should be considered.

10.4.2 Contraception guidance

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS)[c] • Bilateral tubal occlusion • Azoospermic partner (vasectomized or due to a medical cause) *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.* *Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.*
Highly Effective Methods[b] That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] - oral - intravaginal - transdermal - injectable • Progestogen-only hormone contraception associated with inhibition of ovulation[c] - oral - injectable • Sexual abstinence *Sexual abstinence is* considered *a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*

a Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

b Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

c If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure with friction).

10.5 APPENDIX 5: GENETICS

Use/Analysis of DNA/RNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be

due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA/RNA analysis from consenting participants.

- DNA/RNA samples will be used for research related to tusamitamab ravtansine or advanced solid tumor and related diseases. They may also be used to develop tests/assays including diagnostic tests related to CEACAM5 targeting drug and advanced solid tumor. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome (as appropriate).
- DNA/RNA samples will be analyzed for determination of tumor mutation profile on plasma cfDNA and tumor DNA/RNA. Subtractive mutation analysis will be performed with germline DNA data to identify tumor-specific somatic genetic aberrations.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to tusamitamab ravtansine or study interventions of this class to understand study disease or related conditions.
- The results of genetic analyses may be reported in the clinical study report (CSR) or in a separate study summary.
- The Sponsor will store the DNA/RNA samples in a secure storage space with adequate measures to protect confidentiality.

10.6 APPENDIX 6: RECOMMENDED SUPPORTIVE CARE AND/OR DOSE MODIFICATION GUIDELINES FOR DRUG-RELATED ADVERSE EVENTS

Table 15 - Recommended dose modification or discontinuation for tusamitamab ravtansine

Event	Symptoms severity (NCI-CTCAE v5.0)	Dose modification (tusamitamab ravtansine)	Dose modification (gemcitabine)	Supportive care guidelines
Infusion-related reaction	Grade 1-2 eg, Grade ≤2 nausea, headache, tachycardia, hypotension, rash, shortness of breath.	Interrupt tusamitamab ravtansine infusion. Tusamitamab ravtansine may be resumed only after participant recovery, at half the previous infusion rate[a].	Interrupt gemcitabine infusion and start appropriate treatment. Reduce infusion rate by 50%	Give diphenhydramine 50 mg IV and/or dexamethasone 10 mg IV. Dexamethasone can be added as premedication for upcoming cycles for tusamitamab ravtansine

Event	Symptoms severity (NCI-CTCAE v5.0)	Dose modification (tusamitamab ravtansine)	Dose modification (gemcitabine)	Supportive care guidelines
	Grade 3-4 eg, symptomatic bronchospasm, urticaria lesions covering >30% BSA, hypotension, angioedema.	Interrupt tusamitamab ravtansine infusion and definitively discontinue tusamitamab ravtansine.	Interrupt gemcitabine infusion and definitively discontinue gemcitabine	Give diphenhydramine 50 mg IV and/or dexamethasone 10 mg IV and/or epinephrine and any required treatment per Investigator judgment.
Ocular toxicity: Keratopathy/keratitis[b] associated with tusamitamab ravtansine	Grade 1 Asymptomatic, Corneal lesions only observed on routine ocular examination and not requiring topical treatment.	Next infusion of tusamitamab ravtansine at the same dose, with or without cycle delay, depending on the recommendation from the ophthalmologist (nature and extent of the lesion).	Administer gemcitabine as planned	Standard ocular examination is planned as recommended by the ophthalmologist.
	Grade 2 Symptomatic, moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline)	1st episode: tusamitamab ravtansine cycle delay until resolution to Grade 1 (asymptomatic) and restart tusamitamab ravtansine at the same dose. 2nd episode: delay cycle until resolution to Grade 1 (asymptomatic) and tusamitamab ravtansine dose reduction.	Administer gemcitabine the same day as tusamitamab ravtansine	Standard ocular examination weekly until resolution[c d]. Start curative treatment per ophthalmologist recommendation. After resuming study treatment, participant should be followed with standard ocular examination by every two cycles, even asymptomatic during next four cycles. If no recurrence, standard process with follow-up with ocular symptom is resumed. Management of study drug and follow-up process upon recurrence to be discussed according to Grade of the event at recurrence, clinical benefit from study drug and recommendation from the ophthalmologist.
	Grade 3 Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200); corneal ulcer; limiting self-care ADL.	1st episode: tusamitamab ravtansine cycle delay until resolution (asymptomatic) and restart tusamitamab ravtansine with dose reduction. 2nd episode: definitive discontinuation of tusamitamab ravtansine.	Administer gemcitabine as planned if definitive discontinuation of tusamitamab ravtansine	

Event	Symptoms severity (NCI-CTCAE v5.0)	Dose modification (tusamitamab ravtansine)	Dose modification (gemcitabine)	Supportive care guidelines
	Grade 4 Perforation, best corrected visual acuity of 20/200 or worse in the affected eye	Definitive discontinuation of tusamitamab ravtansine.	Administer gemcitabine as planned.	Complete the corneal examination as recommended by ophthalmologist. Repeat the standard ocular examination weekly[c] until resolution[d]. Start curative treatment per ophthalmologist recommendation.
Conduction disorder associated with tusamitamab ravtansine	Grade 1 Mild symptoms	tusamitamab ravtansine administration to be continued upon decision by the Investigator and Sponsor, depending on the nature of the conduction disorder.	No action	ECG performed once weekly until event resolution. Additional evaluations such as LVEF and Holter monitoring should be performed when relevant.
	Grade ≥2	Definitive discontinuation of tusamitamab ravtansine.	No action	ECG to be repeated twice weekly until event resolution. Prompt cardiology consultation Additional evaluations such as LVEF and Holter monitoring should be performed when relevant.
	Grade≥3	Definitive discontinuation of tusamitamab ravtansine.	Decrease gemcitabine to next lower dose level per Table 8	
	Grade≥4	Definitive discontinuation of tusamitamab ravtansine.	Definitive discontinuation of gemcitabine	

Event	Symptoms severity (NCI-CTCAE v5.0)	Dose modification (tusamitamab ravtansine)	Dose modification (gemcitabine)	Supportive care guidelines
Neutrophil count decreased	Grade 1 <LLN-1500/mm^3 ; <LLN-1.5 × 10^9/L	No change in tusamitamab ravtansine administration.	No change in gemcitabine administration	No intervention.
	Grade 2 <1500-1000/mm^3; <1.5-1.0 × 10^9/L	Delay the cycle until recovery of ANC ≥ 1500/mm^3. Restart at the same dose.	No change in gemcitabine administration	No intervention.
	Grade 3 <1000-500/mm^3; <1.0-0.5 × 10^9/L Or Grade 4 (≤7 days) <500/mm^3; <0.5 × 10^9/L	Delay the cycle. Restart the treatment when ANC ≥1500/mm^3 at the same dose on the same day as gemcitabine (only for Cohort C). Prophylactic G-CSF can be considered in all subsequent cycles	Delay the cycle and administer on the same day as tusamitamab ravtansine when ANC ≥1500/mm^3 on **Day 1 and Day 15**, until ANC ≥1000/mm^3 on **Day 8,** at dose reduced per Table 8 Administer prophylactic G-CSF and in all subsequent cycles.	Follow ASCO guidelines on usage G-CSF and antibiotherapy (25). Repeat the test every 3 days.
	Grade 4 >7 days <500/mm^3; <0.5 × 10^9/L	Delay the cycle until ANC ≥1500/mm^3. 1st episode: administer next cycle at the same dose and administer growth factors 2nd episode: administer tusamitamab ravtansine at reduced dose 3rd episode: definitive discontinuation	1st episode: Delay the cycle and administer on the same day as tusamitamab ravtansine when ANC ≥1500/mm^3 on **Day 1 and Day 15**, until ANC ≥1000/mm^3 on **Day 8,** at dose reduced per Table 8 Administer prophylactic G-CSF and in all subsequent cycles. 2nd episode: Delay the cycle and administer on the same day as tusamitamab ravtansine when ANC ≥1500/mm^3 on **Day 1 and Day 15**, until ANC ≥1000/mm^3 on **Day 8,** and decrease 2 dose levels per Table 8. Administer prophylactic G-CSF and in all subsequent cycles. 3rd episode: definitive discontinuation	Follow ASCO guidelines on usage of G-CSF and antibiotherapy (25). Repeat the test every 3 days.

Event	Symptoms severity (NCI-CTCAE v5.0)	Dose modification (tusamitamab ravtansine)	Dose modification (gemcitabine)	Supportive care guidelines
Febrile neutropenia	Grade 3 Absolute neutrophil count <1000/mm^3 with a single temperature of >38.3ºC (101ºF) or a sustained temperature of ≥38ºC (100.4ºF) for more than 1 hour	Delay cycle until ANC >1500/mm^3. 1st episode: administer next cycle at the same dose and administer G-CSF 2nd episode: administer tusamitamab ravtansine at reduced dose 3rd episode: definitive discontinuation	1st episode: Delay the cycle and administer when ANC ≥1500/mm^3 on **Day 1 and Day 15**, until ANC ≥1000/mm^3 on **Day 8,** and decrease to next lower dose level per Table 8 Administer prophylactic G-CSF and in all subsequent cycles. 2nd episode: Delay the cycle and administer when ANC ≥1500/mm^3 on **Day 1 and Day 15**, until ANC ≥1000/mm^3 on **Day 8,** and decrease 2 dose levels per Table 8 (to 600 mg/m^2) Administer prophylactic G-CSF and in all subsequent cycles. 3rd episode: definitive discontinuation	To ensure relative dose intensity, G-CSF is recommended as secondary prophylaxis in all participants with Grade ≥3 febrile neutropenia ASCO guideline is recommended for supportive treatment if there are no defined clinical standards (25).
	Grade 4 Life-threatening consequences	Administration changes to be decided at the Investigator's discretion. 1st episode: administer next cycle at reduced dose and administer G-CSF or definitively discontinue 2nd episode: definitive discontinuation	1st episode: Delay the administration until ANC ≥1500/mm^3 on **Day 1 and Day 15**, until ANC ≥1000/mm^3 on **Day 8,** and decrease to next lower dose level per Table 8. Administer prophylactic G-CSF and in all subsequent cycles. 2nd episode: Definitive discontinuation.	To ensure relative dose intensity, G-CSF is recommended as secondary prophylaxis in all participants with Grade ≥3 febrile neutropenia ASCO guideline is recommended for supportive treatment if there are no defined clinical standards (25).
Thrombocytopenia	Grade 1 Platelets <LLN-75 000/mm^3; <LLN-75.0 × 10^9/L	Delay until platelets ≥100.0 × 10^9/L. Restart at the same dose.	Delay the administration until platelets ≥100.0 × 10^9/L on **Day 1 and Day 15,** administer gemcitabine as planned on **Day 8**. Restart at the same dose.	No intervention.

Event	Symptoms severity (NCI-CTCAE v5.0)	Dose modification (tusamitamab ravtansine)	Dose modification (gemcitabine)	Supportive care guidelines
	Grade 2 Platelets <75 000-50 000/mm^3; <75.0-50.0 × 10^9/L	Delay until recovery of platelets ≥100.0 × 10^9/L. Restart at the same dose.	Delay the administration until platelets ≥100.0 × 10^9/L on **Day 1 and Day 15**, until platelets ≥75.0 × 10^9/L on **Day 8,** and decrease to next lower dose level per Table 8.	No intervention.
	Grade≥3 Platelets <50 000/mm^3; <50.0 × 10^9/L	Administration changes to be decided at the Investigator's discretion. 1st episode: administer next cycle at reduced dose or definitively discontinue 2nd episode: definitive discontinuation	1st episode: Delay the administration until platelets ≥100.0 × 10^9/L on **Day 1 and Day 15**, until platelets ≥75.0 × 10^9/L on **Day 8,** and decrease to next lower dose level per Table 8. 2nd episode: definitive discontinuation.	Additional hematology tests will be done every 2-3 days until recovery to baseline value. Platelet transfusions can be considered per clinical practice.
Hepatic enzyme increase	Grade 1-2	Administer tusamitamab ravtansine as planned.	Administer gemcitabine as planned	No intervention.
	Grade 3	Delay the cycle. Restart the treatment until recovery to Grade 1.	Withhold gemcitabine until recovery to Grade 1 and decrease to next lower dose level per Table 8	Additional liver function tests will be done every 2-3 days until recovery to baseline value.
	Grade 4	Tusamitamab ravtansine should be permanently discontinued.	Gemcitabine should be permanently discontinued.	Additional liver function tests will be done every 2-3 days until recovery to baseline value.
Peripheral neuropathy	Grade 1 Asymptomatic	No action	No action	Participant who has ongoing grade 1 neuropathy has high risk of worsening of his/her symptoms and should be closely followed.
	Grade 2 Moderate symptoms; limiting instrumental Activities of Daily Living	Delay cycle, dose reduction if no improvement with dose delay	No action	
	Grade 3 Severe symptoms; limiting self-care Activities of Daily Living	Definitive discontinuation	No action	

Event	Symptoms severity (NCI-CTCAE v5.0)	Dose modification (tusamitamab ravtansine)	Dose modification (gemcitabine)	Supportive care guidelines
	Grade 4 Life-threatening consequences; urgent	Definitive discontinuation	No action	
Hemorrhage	Grade 3	Definitive discontinuation	Decrease gemcitabine to next lower dose level per Table 8	
	Grade 4	Definitive discontinuation	Definitive discontinuation of gemcitabine	

ASCO = American Society of Clinical Oncology, ASOCT = Anterior segment optical coherence, BSA = Body surface area, ECG = Electrocardiogram, G-CSF = Granulocyte colony-stimulating factor, Hb = Hemoglobin, IMP = Investigational medicinal product, IV = Intravenous; LLN = Lower limit of normal, LVEF = Left ventricular ejection fraction, NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events, RBC = Red blood cell.

a Tusamitamab ravtansine is stable at least 7.5 hours in the infusion bag at room temperature. If necessary, a new infusion should be prepared with the remaining dose to be administered.

b The NCI-CTCAE v5.0 grading is to be applied to keratopathy.

c Standard ocular examination per protocol includes visual acuity, slit-lamp examination, Schirmer's test, and enquiring for ocular/visual symptoms.

d When possible at the site, photographs should be done when findings are first documented and to follow progression when relevant. Any additional relevant ocular examination can be done if indicated.

10.7 APPENDIX 7: AES, ADES, SAES, SADES, USADES AND DEVICE DEFICIENCIES: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING IN MEDICAL DEVICE STUDIES

Not applicable.

10.8 APPENDIX 8: COUNTRY-SPECIFIC REQUIREMENTS

Not applicable.

10.9 APPENDIX 9: CONTINGENCY MEASURES FOR A REGIONAL OR NATIONAL EMERGENCY THAT IS DECLARED BY A GOVERNMENTAL AGENCY

Continuation of the study in the event of a regional or national emergency declared by a governmental agency:

A regional or national emergency declared by a governmental agency (eg, public health emergency, natural disaster, pandemic, and terrorist attack) may prevent access to the clinical trial site.

Contingency procedures are suggested below and in Section 5.5, Section 7.1.2, Section 8, Section 9.3.5, and Section 10.1.3 for an emergency that prevents access to the study site, to ensure the safety of the participants, to consider continuity of the clinical study conduct, protect trial integrity, and assist in maintaining compliance with GCP in Conduct of Clinical Trials Guidance. Sponsor agreement MUST be obtained prior to the implementation of these procedures for the duration of the emergency.

During the emergency, if the site will be unable to adequately follow protocol mandated procedures, alternative treatment outside the clinical trial should be proposed, and prescreening/screening/enrollment/administration of study intervention may be temporarily delayed/halted (see Section 5.5).

Attempts should be made to perform all assessments in accordance with the approved protocol to the extent possible. In case this is not possible due to a temporary disruption caused by an emergency, focus should be given to assessments necessary to ensure the safety of participants and those important to preserving the main scientific value of the study.

Contingencies implemented due to emergency will be documented.

10.9.1 Remote prescreening process

If there is no other way to conduct prescreening procedures during a regional or national emergency declared by a governmental agency (eg, due to a COVID-19 pandemic), the site may consider implementing a remote prescreening ICF process compliant with country/site requirements for only those participants who have enough archival samples.

The process should be compliant with accepted principals of patients' rights and global, national, and local regulatory requirements. Required protection of personal data (including security of e-mail interactions) and confidentiality of study data should be ensured.

If remote prescreening is planned to be implemented at site:

- The Investigator/delegate should contact each participant to inquire regarding the participant's willingness to participate in the prescreening process.
- If participant agrees to prescreening, the Investigator/delegate should send the prescreening ICF via e-mail to the participant's personal e-mail address (as allowed by local regulation) or by postal mail. The Investigator/delegate should provide an overview of the study (eg, tusamitamab ravtansine mechanism of action; design of the study in terms of treatment groups, visits, and prescreening procedures; and rationale for assessment of CEACAM5 expression). The Investigator/delegate should respond to any question raised by a participant, and this correspondence should be documented in detail in the participant's source file.
- If a participant agrees to participate in the prescreening phase, the participant should print out, sign, and date 2 copies of the ICF. A scan of a signed ICF should be sent via secured e-mail (if available), and 1 of the signed original ICFs to be filed in the Investigator Study File should be sent via postal mail.

- The Investigator/delegate should review each received signed ICF (or a printout of an electronically submitted, scanned copy), sign and date it, and archive it in the Investigator Study File. It is mandatory for the Investigator to ensure the collection of the original signed ICF sent by mail; the signed original should be attached to any previously filed signed printout of an electronically submitted signed ICF. After properly documenting this consent process, the site may proceed to prepare and send the slides for CEACAM5 assessment.

10.9.2 Screening procedures

The Investigator/site should assess the site's capacity to conduct study procedures throughout the study for each participant before starting any screening procedure. If the site cannot guarantee an accurate follow-up in the context of the trial, alternative treatment outside the clinical trial should be proposed. This assessment, per the Investigator's medical judgment and depending on the country/site status, should be communicated to the participant. The participant should satisfy all eligibility criteria before enrolling to the study; and no protocol waiver is acceptable. Remote signature of main study ICF is not acceptable in any circumstance.

10.9.3 Study intervention

During a regional or national emergency declared by a governmental agency, all contingency plans should be implemented to ensure compliance to study treatment, based on a case-by-case benefit–risk assessment. Administration (or, in case of temporary interruption, reinitiation) of the IMP can occur only once the Investigator has determined, according to his/her best judgment, that the contribution of the IMP(s) to the occurrence of the epidemic event (eg, COVID-19) was unlikely.

Any further safety measure (eg, interim laboratory assessment such as neutrophil count monitoring; regular contact with site staff) to follow the safety of patients during the regional or national emergency period can be considered.

10.9.4 Study procedures

All efforts should be made to ensure that measurements of key parameters for efficacy endpoints can be performed at the site. If the Investigator is unable to guarantee that the protocol-required efficacy assessments can be conducted, no participant should be screened until the site confirms its capacity to perform the assessments.

As part of a site's contingency plan, a back-up site should be identified in advance in the case that the site delegated to perform the radiological tumor assessment is prevented from performing the assessment by a regional or national emergency situation (eg, COVID-19 outbreak). The Investigator should ensure that the back-up site conducts the RECIST assessment in same manner as that used for baseline tumor assessments.

In the case that the primary tumor assessment site is incapacitated, ongoing patients would then be referred to the back-up site for tumor assessment. The Investigator/delegate should ensure the

information on baseline assessment methods is shared with the back-up site's radiologist to ensure same method is followed for scans.

Depending on on-site status, if needed, Cycle 1 and Cycle 2 weekly safety laboratory assessment for Cohorts A and B (hematology [hemoglobin, hematocrit, RBC, WBC with differential, and platelet counts] and liver function tests [AST, ALT, total and direct bilirubin, ALP]) can be arranged to be performed either at a laboratory certified to perform these tests that is close to the patient's home, or via sampling at the patient's home.

10.9.5 Statistical analyses and deviation

The impact of the regional or national emergency declared by a governmental agency on study conduct will be summarized (eg, study discontinuation or discontinuation/delay/omission of the intervention due to the emergency). Any additional analyses and methods required to evaluate the impact on efficacy (eg, missing data due to the emergency) and safety will be detailed in the SAP.

10.9.6 Informed consent process

For a regional or national emergency declared by a governmental agency, contingency procedures may be implemented for the duration of the emergency. The participant or legally authorized representative should be informed verbally prior to initiating any change that is to be implemented for the duration of the emergency (eg, study visit delays, use of back-up sites for safety laboratory or tumor assessment).

10.10 APPENDIX 10: CYP SUBSTRATES WITH NARROW THERAPEUTIC RANGE AND STRONG CYP3A INHIBITORS

Table 16 - List of CYP substrates with narrow therapeutic range

***In vivo* CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A Narrow Therapeutic Range (NTR) Substrates**	
CYP enzyme	NTR Substrates[a]
CYP1A2	Theophylline, tizanidine
CYP2C8	Paclitaxel
CYP2C9	Warfarin, phenytoin
CYP2C19	S-mephenytoin
CYP2D6	Thioridazine
CYP3A	Alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, quinidine, sirolimus, tacrolimus, cisapride, astemizole, terfenadine, pimozide

a CYP Substrates with a narrow therapeutic range - drugs with an exposure-response relationship that indicates that relatively small increases in their exposure levels by co-administered CYP inhibitors may lead to safety concerns.

Table 17 - List of strong CYP3A inhibitors

STRONG CYP3A INHIBITORS			
CYP3A inhibitors	**Precipitant Therapeutic Class**	**Victim (oral, unless otherwise specified)**	**AUC Ratio**
Potent CYP3A Inhibitors (yielding substrate AUC ratio >5)			
VIEKIRA PAK	antivirals	tacrolimus	55.76
telaprevir	antivirals	midazolam	13.5
indinavir/rit	protease inhibitors	alfentanil	36.50
tipranavir/rit	protease inhibitors	midazolam	26.91
ritonavir	protease inhibitors	midazolam	26.41
cobicistat	pharmacokinetic enhancer	midazolam	19.03
indinavir	protease inhibitors	vardenafil	9.67
ketoconazole	antifungals	midazolam	17.08
troleandomycin	antibiotics	midazolam	14.80
saquinavir/rit	protease inhibitors	midazolam	12.48
itraconazole	antifungals	midazolam	10.80
voriconazole	antifungals	midazolam	9.63
mibefradil	calcium channel blockers	midazolam	8.86
clarithromycin	antibiotics	midazolam	8.39
danoprevir/rit	antivirals	midazolam	13.42
lopinavir/rit	protease inhibitors	alfentanil	11.47
elvitegravir/rit	treatments of AIDS	midazolam	12.8
posaconazole	antifungals	midazolam	6.23
telithromycin	antibiotics	midazolam	6.2
conivaptan	vasopressin antagonists	midazolam	5.76
nefazodone	antidepressants	midazolam	5.44
nelfinavir	protease inhibitors	midazolam	5.29
saquinavir	protease inhibitors	midazolam	5.18
boceprevir	antivirals	midazolam	5.05
idelalisib	kinase inhibitors	midazolam	5.15
LCL161	cancer treatments	midazolam	8.80
mifepristone	antiprogestins	simvastatin	9.55
ceritinib	kinase inhibitors	midazolam	5.42
ribociclib	kinase inhibitors	midazolam	5.17
josamycin	antibiotics	ivabradine	7.70
tucatinib	kinase inhibitors	midazolam	5.74
lonafarnib	other	midazolam	7.39

List extracted from the Drug Interaction Database from the University of Washington (Home Page: www.druginteractioninfo.org; https://didb.druginteractionsolutions.org/resources/list-of-substrates-inhibitors-and-inducers/?Oid=1130), updated in January 2022 and from FDA (https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm) updated in June 2020.
Abbreviations: AIDS = acquired immune deficiency syndrome, AUC = area under the curve, CYP = cytochrome P450, RIT = ritonavir.

10.11 APPENDIX 11: RESPONSE EVALUATION CRITERIA IN SOLID TUMORS VERSION 1.1

Details provided in bibliographic reference (27).

10.11.1 Measurability of tumor at baseline

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as follows.

Measurable lesions must be accurately measured in at least 1 dimension (longest diameter in the plane of the measurement to be recorded) with a minimum size of:

- 10 mm by CT-scan (CT-scan slice thickness no greater than 5 mm).
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in the short axis when assessed by CT-scan (CT-scan slice thickness recommended to be no greater than 5 mm). At baseline and at follow-up, only the short axis will be measured and followed.

Non-measurable lesions are all other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), as well as truly non-measurable lesions. Lesions considered non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, and abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

10.11.2 Special considerations regarding lesion measurability

- **Bone lesions:**

1. Bone scan, positron emission tomography scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
2. Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
3. Blastic bone lesions are non-measurable.

- **Cystic lesions**:

1. Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
2. "Cystic lesions" thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same participant, these are preferred for selection as target lesions.

- **Lesions with prior local treatment:**

1. Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

Method of assessment

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation should always be performed rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical examination.

- **Clinical lesions:** Clinical lesions will only be considered measurable when they are superficial and ≥10 mm diameter as assessed using calipers. For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may be reviewed at the end of the study.
- **Chest X-ray:** Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.
- **CT, MRI:** CT is the best currently available and reproducible method to measure lesions selected for response assessment. Measurability of lesions on CT-scan is based on the assumption that CT slice thickness is 5 mm or less. When CT-scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.
- **Ultrasound:** Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.
- **Endoscopy, laparoscopy:** The utilization of these techniques for objective tumor evaluation is not advised.

- **Tumor markers:** Tumor markers alone cannot be used to assess objective tumor response.
- **Cytology, histology:** These techniques can be used to differentiate between PR and CR in rare cases if required by protocol.

Baseline documentation of "target" and "non-target" lesions

When more than 1 measurable lesion is present at baseline all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline.

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and should lend themselves to reproducible repeated measurements.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15 mm by CT-scan. Only the short axis of these nodes will contribute to the baseline sum. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should not be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present", "absent", or "unequivocal progression". In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case (eg, "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

Response criteria

Response criteria are described in Table 18.

Table 18 - Response criteria

Response criteria	Evaluation of target lesions
CR	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
PR	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters.
PD	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of 1 or more new lesions is also considered progression).
SD	Neither sufficient shrinkage from the baseline study to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study.

Abbreviations: CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease.

Special notes on the assessment of target lesions

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded and should be measured in the same anatomical plane as the baseline examination, even if the nodes regress to <10 mm on study. This means that when lymph nodes are included as target lesions, the "sum" of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of <10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become "too small to measure": All lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT-scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being "too small to measure". When this occurs it is important that a value be recorded on the CRF. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned.

When non-nodal lesions "fragment", the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the "coalesced lesion".

Evaluation of non-target lesions

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

- CR: Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).
- Non-CR/Non-PD: Persistence of 1 or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- Progressive Disease: Unequivocal progression of existing non-target lesions. (Note: the appearance of 1 or more new lesions is also considered progression).

The concept of progression of non-target disease requires additional explanation as follows:

When the participant also has measurable disease; in this setting, to achieve "unequivocal progression" on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of 1 or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.

When the participant has only non-measurable disease; to achieve "unequivocal progression" on the basis of the non-target disease, there must be an overall level of substantial worsening such that the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of 1 or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing participants for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in "volume" (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from "trace" to "large", an increase in lymphangitic disease from localized to widespread, or may be described in protocols as "sufficient to require a change in therapy". If "unequivocal progression" is seen, the participant should be considered to have had overall PD at that point.

New lesions

The appearance of new malignant lesions denotes disease progression. The finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the participant's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT-scan report as a "new" cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the participant who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The participant's brain metastases are considered to be constitute PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents new disease. If repeat scans confirm that there is a new lesion, then progression should be declared using the date of the initial scan.

While fluorodeoxyglucose-positron emission tomography (FDG-PET) response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT-scanning in assessment of progression (particularly possible "new" disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

1. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
2. No FDG-PET at baseline and a positive FDG-PET at follow-up.

If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.

If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT-scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Evaluation of best overall response

Time point response: At each protocol-specified time point, a response assessment should occur. Table 19 provides a summary of the overall response status calculation at each time point for participants who have measurable disease at baseline.

Table 19 - Response in participants with target disease

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	Inevaluable
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease.

When participants have non-measurable (therefore non-target) disease only, Table 20 is to be used.

Table 20 - Response in participants with non-target disease only

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD
Not all evaluated	No	Inevaluable
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease.

Missing assessments and inevaluable designation: When no imaging/measurement is done at all at a particular time point, the participant is not evaluable (NE) at that time point.

If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD.

Special notes on response assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that participants with CR may not have a total sum of "zero" on the CRF.

In trials where confirmation of response is required, repeated "NE" time point assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials it is reasonable to consider a participant with time point responses of PR-NE-PR as a confirmed response.

Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy.

The objective response status of such participants is to be determined by evaluation of target and non-target disease. For equivocal findings of progression (eg, very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

Duration of response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or PD is objectively documented (taking as reference for PD the smallest measurements recorded on study).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

Reproduced from: Eisenhauer EA, Therasse P, Bogaerts J et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228-47. (27).

10.12 APPENDIX 12: ABBREVIATIONS

ADC:	antibody-drug conjugate
AE:	adverse event
AESI:	adverse event of special interest
AIDS:	acquired immunodeficiency syndrome
ALT:	alanine aminotransferase
ANC:	absolute neutrophil count
AP:	alkaline phosphatase
ASCO:	American Society of Clinical Oncology
AST:	aspartate aminotransferase
ATA:	anti-therapeutic antibodies
BOR:	best overall response
BSA:	body surface area
BUN:	blood urea nitrogen
CEA:	carcinoembryonic antigen
CEACAM5:	carcinoembryonic antigen-related cell adhesion molecule 5
cfDNA:	circulating free deoxyribonucleic acid
CI:	confidence interval
COVID-19:	Coronavirus Disease
CR:	complete response
CRF:	case report form
CSICF:	Core Study Informed Consent Form
CT:	computed tomography
CTC:	circulating tumoral cells
CTCAE:	Common Terminology Criteria for Adverse Events
CYP450:	Cytochrome P450

DCR:	disease control rate
DL:	dose level, dose level
DLT:	dose-limiting toxicity
DM4:	ravtansine
DNA:	deoxyribonucleic acid
DOR:	duration of response
ECG:	electrocardiogram
ECOG:	Eastern Cooperative Oncology Group
eCRF:	electronic case report form
eGFR:	estimated glomerular filtration rate
EOT:	end-of-treatment
FDA:	United States Food and Drug Administration
FDG-PET:	fluorodeoxyglucose-positron emission tomography
FFPE:	formalin-fixed, paraffin embedded
GCP:	Good Clinical Practice
G-CSF:	granulocyte colony-stimulating factor
GDPR:	General Data Protection Regulation
HCV:	hepatitis C virus
HER2:	human epidermal growth factor receptor 2
HIV:	human immunodeficiency virus
HRT:	hormone replacement therapy
IB:	Investigator's Brochure
ICF:	Informed Consent Form
ICH:	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC:	Independent Ethics Committees
IHC:	immunohistochemistry
IRB:	Institutional Review Board
IRT:	interactive response technology
IV:	intravenous, intravenous
LDH:	lactate dehydrogenase
mBC:	metastatic breast cancer
MDRD:	modification of diet in renal disease
MedDRA:	medical dictionary for regulatory activities
mPAC:	metastatic pancreatic adenocarcinoma
MRI:	magnetic resonance imaging
MTD:	maximum tolerated dose, maximum tolerated dose
NCI:	National Cancer Institute
NE:	not evaluable
NIMP:	noninvestigational medicinal product
NSCLC:	non-small-cell lung carcinoma
NSQ:	non-squamous
ORR:	objective response rate
OS:	overall survival
PAC:	pancreatic adenocarcinoma
PD1:	programmed cell death protein 1

PD-L1:	programmed death-ligand 1
PFS:	progression-free survival
PR:	partial response
PT:	preferred term
Q2W:	every 2 weeks, every 2 weeks, every 2 weeks, every 2 weeks, every 2 weeks, every 2 weeks
RECIST:	Response Evaluation Criteria In Solid Tumors
RNA:	ribonucleic acid
SAE:	serious adverse event
SAP:	statistical analysis plan
SD:	source document
SoA:	Schedule of Activities
SOC:	system organ class
TEAE:	treatment-emergent adverse event
TNBC:	triple-negative breast cancer
ULN:	upper limit of normal
US:	United States
WBC:	white blood cell
WOCBP:	woman of childbearing potential

10.13 APPENDIX 13: PROTOCOL AMENDMENT HISTORY

This is the second protocol amendment. Details of this amendment are detailed in the Protocol Amendment Summary of Changes preceding the Table of Contents. Details of amended protocol 01 are presented in this section.

AMENDMENT 01 (01 October 2021)

This amended protocol 01 (amendment 01) is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The purpose of this amendment is to cancel the interim analysis after ten participants treated and to continue enrolling and treating pancreatic cancer patients who have been prescreened and have CEACAM5 positive. Here are the reasons:

- The prescreening was higher and faster than expected, so the prescreening was stopped in July 2021.

- The incidence of high CEACAM5 expression was greater than initially expected; approximately 40% instead of 15%.

- Given the very limited treatment options in these patients along with the unmet medical need of this population, patients with positive CEACAM5 expression should be allowed to continue participation in this study.

- The interim analysis was removed in order to better assess the efficacy in this patient population in a larger sample size.

Beside this change, further modifications to protocol wording were implemented, as detailed below.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Cover page	INN name, tusamitamab ravtansine was added	The newly approved INN name was added
	NCT number added	NCT number is available
1.1 Synopsis (Intervention groups and duration), 1.3 Schedule of activities (SoA) (footnote 'b' for screening)	Deleted the suggestion for consideration of approximately 10 days between screening visit and initiation of therapy.	Backup IMP available at sites
1.1 Synopsis (objectives and endpoints), 3 Objectives and endpoints	Added the word "confirmed" for CR and PR for DCR and DOR definitions	To clarify
1.1 Synopsis (Premedication), 6.1 Study intervention(s) administered	"15 minutes to"; "depending on the administration form IV or oral [15 minutes prior for IV and 1 hour prior for oral]" were added	To provide detailed NIMP instructions
1.1 Synopsis, 9.3.1 General considerations, 9.4 Interim Analyses	Added confirmatory assessment of tumor assessment for interim analysis and primary analysis	To clarify
1.2 Schema	Updated details for cohort B	To reflect the change of removing the interim analysis for the pancreas cohort
1.3 Schedule of activities (SoA), 8 Study Assessments and Procedures, 8.6.1 Pharmacodynamics	Added circulating CEA during prescreening	To evaluate circulating CEA levels at prescreening
1.3 Schedule of activities (SoA) (footnote 'l' for Tumor assessment), 8.1 Efficacy assessments	Added text to continue tumor assessment until death, withdrawal of participant's consent, or study cut-off date for secondary efficacy endpoints, whichever comes first.	To clarify
	Deleted option for tumor assessment every 12 weeks for new anti-cancer therapy patients 'if the discontinuation is due to other reason than progressive disease'	To clarify

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of activities (SoA)	Added window period for tumor assessments in footnote 'l'	To clarify
3 Objectives and endpoints	Added "and to evaluate circulating CEA levels at prescreening" to tertiary/exploratory objectives	To evaluate circulating CEA levels at prescreening
4.2 Scientific Rationale for Study Design, 9.4 Interim analyses	Removed specifications of interim analysis planning for the pancreas cohort and deleted "For the mPAC cohort, if no confirmed response is observed among the first 10 treated participants evaluable for activity, the cohort will be closed."	To remove the interim analysis for the pancreas cohort and continue enrolling and treating pancreatic cancer patients who have been prescreened and have CEACAM5 positive
4.2 Scientific Rationale for Study Design, 9.3.1 General considerations, 9.4 Interim analyses	Removed specifications of interim analysis in mPAC cohort "and 10 treated evaluable participants in mPAC cohort"	To continue screening and treating pancreatic cancer patients
5.2 Exclusion Criteria	Deleted specification for German sites in E07	Not applicable as German site are not in the study
5.4 Screen Failures	Clarified re-screening process	To clarify
8.3 Adverse events (AEs), Serious adverse events (SAEs) and Other Safety Reporting	Added reference to protocol sections for definitions, method of recording, evaluating, and assessing causality of AEs, SAEs, and AESIs.	To clarify
8.3.1 Time period and frequency for collecting AE and SAE information	Updated collection of AEs and SAEs from screening instead of prescreening.	To clarify
	Added text for collection of only AEs related to fresh biopsy procedure at prescreening.	To clarify
8.3.5 Pregnancy	Added text for follow up of outcome of the pregnancy, post-study pregnancy-related SAE, and discontinue study intervention or be withdrawn from study on pregnancy.	To clarify
8.3.10.6 Peripheral neuropathy	New section with guidance for managing peripheral neuropathy.	For clarity of safety management guidelines.
8.3.10.7 Colitis (including hemorrhagic)	New section for managing GI toxicity.	For clarity of safety management guidelines.
8.9 Use of biological samples and data for future research	The phrase "drug response and toxicity" is replaced with "mechanism of action, or possible toxicity".	Updated as per new template text
	Added text for collection and utilization of remaining leftover samples and additional/extra samples.	Updated as per new template text
	Updated time frame for storage of relating data and biological samples for future research from 15 years to 25 years.	Updated as per new template text
	Deleted text for storage of study participant coded data.	Updated as per new template text

Section # and Name	Description of Change	Brief Rationale
9.2 Populations for Analyses	Updated definition of activity population	To clarify
	Deleted text for concomitant consideration of CEACAM5 positivity for screened participant population.	Updated to take into all CEACAM5 patients in screened population.
	Added text for exclusion of participants exposed to study intervention before or without being enrolled, from analysis populations and only to be considered in safety population.	To clarify
	Added below text: Enrolled participants for whom it is unclear whether they took the study intervention will be considered as exposed and will be included in the safety population. For any participant enrolled more than once, only the data associated with the first enrollment will be used in any analysis population. The safety experience associated with any later enrollment will be reported separately.	To clarify
10.1.3 Informed consent process	Updated ICF process for re-screening	For clarity
	Deleted repeated wording from section 5.4	For clarity
10.1.7 Data quality assurance	Removed the paragraph of quality tolerance limits	Not applicable
10.6 Appendix 6: Recommended supportive care and/or dose modification guidelines for drug-related adverse events	New section for managing hemorrhage.	For clarity of safety management guidelines.
10.10 Appendix 10: CYP substrates with narrow therapeutic range and strong CYP3A inhibitors, Table 13	Updated list of strong CYP3A inhibitors	Drug interaction list updated
Throughout	Minor editorial, typographical error corrections and standardization of wording	For clarity
	SAR408701 replaced by tusamitamab ravtansine	The approved product name was added

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