AMENDED CLINICAL TRIAL PROTOCOL 06

Protocol title:	**Randomized, open-label, Phase 3 study of SAR408701 versus docetaxel in previously treated, metastatic, nonsquamous, non–small-cell lung cancer patients with CEACAM5-positive tumors**
Protocol number:	**EFC15858**
Amendment number:	**06**
Compound number (INN/Trademark):	**SAR408701 (tusamitamab ravtansine/NA)**
Study phase:	**Phase 3**
Short title:	**SAR408701 versus docetaxel in previously treated, carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5)-positive, metastatic nonsquamous non–small-cell lung cancer patients (CARMEN-LC03)**
Sponsor name:	**Sanofi-aventis recherche & développement**
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Monitoring Team's Representative Name and Contact Information	

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Approval date: 13-Mar-2023 Total number of pages: 133

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/ countries impacted by amendment	Date, version
Amended Clinical Trial protocol 06	All	Date: 13-Mar-2023, version 1 (electronic 10.0)
Amended Clinical Trial protocol 05	All	Date: 18-Oct-2022, version 1 (electronic 9.0)
Amended Clinical Trial protocol 04	All	Date: 21-Jul-2021, version 1 (electronic 5.0)
Amended Clinical Trial protocol 03	All	Date: 20-Jul-2020, version 1 (electronic 4.0)
Amended Clinical Trial protocol 02	All	Date: 13-Dec-2019, version 1 (electronic 3.0)
Amended Clinical Trial protocol 01	All	Date: 27-Sep-2019, version 1 (electronic 2.0)
Original Protocol		Date: 26-June-2019, version 1 (electronic 1.0)

AMENDED PROTOCOL 06 (13-MAR-2023)

This amendment 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 because it may impact the scientific value of the study.

OVERALL RATIONALE FOR THE AMENDMENT

Due to a higher dropout rate for progression-free survival (PFS) than initially assumed, the anticipated number of PFS events by the time of the first interim analysis (IA) of overall survival (OS; with 50% information fraction) planned in amended protocol 05 is anticipated to be significantly lower than the expected 221 PFS events.

To maintain an adequate power for PFS analysis while not considerably delaying the futility analysis on OS planned at the same time, the cut-off date for the first IA of OS is now redefined as the time when approximately 221 PFS events or approximately 210 deaths (approximately 58% information fraction) are observed, whichever comes first. The futility threshold based on the OS hazard ratio to be applied at the time of this analysis is now also updated from 0.95 to 0.90.

Beside these changes, further modifications to protocol wording as detailed in the Summary of Changes table were implemented.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis; 4.4 End of study definition; 9.2 Sample size determination	The information fraction at the first IA of OS was updated from 50% to 58%.	To reflect increased dropout rate for PFS
1.1 Synopsis; 4.4 End of study definition; 9.2 Sample size determination; 9.4 Statistical analyses; 9.5 Interim analyses	Respective cut-off dates for the first IA, second IA, and final analysis of OS were updated from 33 months, 44 months, and 53 months to 40 months, 48 months, and 58 months.	To reflect increased dropout rate for PFS
1.1 Synopsis; 9.2 Sample size determination	The estimated power for the first analysis of OS was updated from 82% to 81%; and the expected number of OS events was increased from 183 deaths to 210 deaths.	To reflect increased dropout rate for PFS
1.1 Synopsis; 9.2 Sample size determination	The PFS probablility of dropout rate by 4 months was updated from 10% to 17%	To reflect the PFS probability of dropout rate
1.1 Synopsis; 9.2 Sample size determination; 9.4.1 Efficacy analyses; 9.5 Interim analyses	Definition of the cut-off date for final analysis of PFS was updated from “total of 221 PFS events (approximate number of PFS events anticipated to be observed when approximately 183 deaths will be observed)” to “approximately 221 PFS events or approximately 210 deaths ... , whichever comes first.”	To reflect increased dropout rate for PFS
1.1 Synopsis; 9.4. Statistical analyses; 9.4.1.1.1 Progression free survival; 9.4.1.1.2 Overall survival	Time from cut-off date for final analysis of PFS to planned cut-off date for final analysis of OS was updated from 20 months to 18 months, and time to cut-off for IA of OS at 80% IF was changed from approximately 11 months to 8 months	To reflect increased dropout rate for PFS
1.1 Synopsis; 9.6 Multiplicity	For overall response rate (ORR) and health-related quality of life (HRQoL) time to deterioration (TTD) endpoints, the Lan-DeMets O'Brien-Fleming α-spending function is replaced by a user-defined α-spending function.	Due to uncertainty regarding the information fraction and overall α level available for testing those key secondary endpoints
1.3.2 Crossover phase; 5.1 Inclusion criteria; 5.2 Exclusion criteria	Modified headers for crossover phase schedule of activities and crossover phase inclusion/exclusion criteria to clarify that these would be implemented only if certain prespecified efficacy criteria are met	To clarify that implementation of the crossover phase is conditional

Section # and Name	Description of Change	Brief Rationale
1.3.2 Crossover phase; 8.2.5 Clinical safety laboratory assessments	Troponin assessments were added to the schedule of activities for the crossover phase, and a corresponding footnote **d** was added to describe details of timing. Statement that troponin would not be assessed in crossover participants was deleted from safety laboratory assessments, and timing of troponin assessments was described here.	To keep same safety measurement as in main study phase
4.1.1 Duration of the study period	Total estimated enrollment duration was updated from 43 months to 50 months.	Updated per realized enrollment
4.1.2 Crossover treatment phase	Added statement that Sponsor will notify sites in writing if the crossover phase is implemented.	To clarify how crossover phase implementation would be communicated to sites
6.6. Dose modification	Dose levels for second dose reductions (requiring case-by-case discussion with sponsor) were added to table, and additional language added to text and table footnote.	For clarity
8.1 Efficacy assessments	Description of tumor assessment procedures for participants who have EOT visits due to reasons other than PD “until documented PD” was corrected by adding “or OS study cut-off”	For clarity
8.2.5 Clinical safety laboratory assessments	Deleted statement that troponin will not be assessed during the crossover treatment phase, and added description of assessments for crossover participants.	To keep same rule of troponin assessment during crossover treatment phase, if implemented
9.2 Sample size determination	Updated previous estimate of enrollment rate from 12 to 10 participants per month, and removed previously provided alternative estimate based on 10 participants per month as redundant.	To reflect new statistical assumption
9.5 Interim analyses	Table 7 was updated with probabilities of crossing the futility boundary.	To reflect updated information fraction due to increased dropout rate for PFS
9.5 Interim analyses	Added statement that predictive power for the final OS analysis given the IA data could be used as supportive information in the futility decision.	To clarify considerations to be used in the futility decision
9.6 Multiplicity	Boundary properties for planned analyses of PFS (Table 8) and OS (Table 9) were updated.	To reflect updated information fraction due to increased dropout rate for PFS
10.1.3 Informed consent process	Deleted erroneous reference to a legally authorized representative.	This reference has been removed as not applicable for this study.

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol title: Randomized, open-label, Phase 3 study of SAR408701 versus docetaxel in previously treated, metastatic, nonsquamous non-small-cell lung cancer patients with CEACAM5-positive tumors

Short title: SAR408701 versus docetaxel in previously treated, carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5)-positive, metastatic, nonsquamous non–small-cell lung cancer patients (CARMEN-LC03)

Rationale:

Despite recent progress in the treatment of advanced non–small-cell lung cancer (NSCLC), there remains a need for effective new treatment at the time of disease progression.

Tusamitamab ravtansine (SAR408701) is an antibody-drug conjugate (ADC) combining hu769_4D4 (SAR408377), a humanized antibody that recognizes selectively the A3-B3 extracellular domain of carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5), a tumor-associated carcinoembryonic antigen, with the potent cytotoxic maytansinoid derivative (DM)4, that inhibits microtubule assembly. SAR408701 is expected to selectively deliver DM4 to cancer cells expressing the CEACAM5 antigen, such as colon, stomach and its signet-ring cell subtype, as well as NSCLC (adenocarcinoma).

Carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5) was first described in 1965 as a tumor-associated antigen in human colon cancer tissue extracts (1). High levels of CEACAM5 expression have since been observed in several epithelial tumors while in normal adult tissue, its expression is limited to few tissues (2, 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, the stomach and its subtype signet ring cell as well as in nonsquamous NSCLC.

In the first-in-human study (TED 13751), a cohort of patients with pretreated nonsquamous NSCLC with membrane CEACAM5 expression ≥2+ in intensity in at least 50% of the tumor cell population were treated with tusamitamab ravtansine at the recommended dose of 100 mg/m² every 2 weeks. Preliminary results on the first 32 evaluable patients treated, showed encouraging antitumor activity and were associated with a response rate of 25% (90% CI 14.70%-39.20%). The accrual continued to obtain 64 patients treated to ensure a minimum of 30 patients pretreated with anti-programmed death 1/program death ligand 1 (PD-1/PD-L1).

Objectives and endpoints

Objectives	Endpoints
Primary	
Study is designed with 2 primary endpoints that will be analyzed on randomized participants at the time of the cut-off date for each given analysis (progression free survival [PFS] and overall survival [OS]). Study success is defined either on PFS or OS.	
• The primary objective is to determine whether tusamitamab ravtansine improves the progression free survival (PFS) when compared to docetaxel in participants with metastatic nonsquamous NSCLC expressing CEACAM5 ≥2+ in intensity in at least 50% of the tumor cell population and previously treated with standard-of-care platinum-based chemotherapy and an immune checkpoint inhibitor (ICI)	• The primary endpoint is PFS as assessed by independent blinded review committee (IRC) and based on RECIST 1.1 assessments. PFS will be defined as the time from randomization to the date of the first documented disease progression or death due to any cause, whichever comes first.
• The primary objective is to determine whether tusamitamab ravtansine improves the overall survival (OS) when compared with docetaxel in participants with metastatic nonsquamous NSCLC expressing CEACAM5 ≥2+ in intensity in at least 50% of the tumor cell population and previously treated with standard-of-care platinum-based chemotherapy and an immune checkpoint inhibitor.	• The primary endpoint is OS and defined as the time from randomization to the date of death due to any cause.
Secondary	
• To compare the objective response rate (ORR) to tusamitamab ravtansine with docetaxel	• Objective response rate will be defined as the proportion of participants who have a complete response (CR) or partial response (PR), as best overall response derived from Overall Response (OR) determined by the IRC per RECIST 1.1
• To compare the health-related quality of life (HRQOL) to tusamitamab ravtansine with docetaxel	• HRQOL will be analyzed through three different endpoints: - Time to deterioration (TTD) in disease related symptoms (composite endpoint of cough, chest pain and dyspnea) as determined by EORTC QLQ-LC13 - TTD in physical function as determined by EORTC QLQ C-30 - TTD in role function as determined by EORTC QLQ C30 The TTD is defined as the time from baseline until the first ≥10 point change from baseline up to the end of treatment.
• To evaluate the safety of tusamitamab ravtansine compared to docetaxel	• Incidence of TEAEs and SAEs and laboratory abnormalities according to NCI CTCAE v5.0
• To assess the duration of response (DOR) to tusamitamab ravtansine as compared with docetaxel	• Duration of response (DOR) is defined as the time from first documented evidence of CR or PR until progressive disease (PD) determined per RECIST 1.1 or death from any cause, whichever occurs first

Overall design:

This is a Phase 3, randomized, open-label, multicenter, efficacy and safety study of tusamitamab ravtansine versus docetaxel in patients with metastatic nonsquamous NSCLC whose tumors express CEACAM5 (measured using the CEACAM5 immunohistochemistry [IHC]769 assay). CEACAM5 positivity in this study is defined as membranous CEACAM5 expression in the most recent formalin-fixed paraffin-embedded (FFPE) archival tumor tissue (or if not available in fresh tumor tissue) sample as ≥2+ in intensity in at least 50% of the tumor cell population, demonstrated prospectively by central IHC evaluation.

Once participants have signed a prescreening informed consent form (ICF), the prescreening phase will correspond to the timing of sending archival tumor material and IHC analyses to allow determination of CEACAM5 status by central laboratory. Prescreening for CEACAM5 status could be performed in advance during prior anticancer therapy. During the study screening phase, only nonsquamous NSCLC CEACAM5 positive participants determined by central assay will go through protocol study procedures.

The study will have 3 main periods: screening, study treatment and follow up. After being screened the eligible patients will be randomized (1:1) to one of the following treatment arms:

- Treatment A: tusamitamab ravtansine every 2 weeks (Q2W cycle) at the dose of 100 mg/m^2.
- Treatment B: docetaxel every 3 weeks (Q3W cycle) at the dose of 75 mg/m^2.

Treatment allocation will be performed by an Interactive Response Technology (IRT). All eligible patients will be randomly assigned to either of the experimental arm or the control arm in a 1:1 proportion. Allocation to the 2 treatment arms will be done using stratified randomization based on Eastern Cooperative Oncology Group (ECOG) performance status (0 versus 1), previous immune checkpoint inhibitors (ICI) treatment (sequential versus combination with chemotherapy) and geographical region (Asia versus Western Europe+Australia+North America versus Rest of the World [RoW]).

Participants will continue to receive their assigned treatment until objective disease progression, unacceptable toxicity, or upon participant's request to stop treatment, or Investigator decision, whichever occurs first.

After discontinuing randomized study intervention, the participant will enter the follow up period. During the follow-up period, participants may be treated with standard of care per investigator discretion, and the details will be collected as post-study treatment. In case the crossover phase is implemented after the time of the 58% interim analysis of OS, participants enrolled to the docetaxel treatment arm may also be allowed to receive crossover treatment with tusamitamab ravtansine after documented disease progression.

The study is designed with 2 primary endpoints that will be analyzed on randomized participants at the time of the cut-off date for each given analysis (PFS and OS). Regardless of the outcome of PFS analysis, enrollment will continue to have the final analysis of OS, unless the result of either interim analysis of OS is overwhelming for efficacy or futility.

An independent DMC will periodically assess the progress of the clinical trial, review the safety data and will advise the study principal Investigator (s) and Sponsor regarding patient safety, as well as the course of action regarding the conduct of the trial. The DMC will also be in charge of reviewing the final analysis of PFS and the formal statistical interim analyses for OS.

An independent radiological review committee (IRC; blinded to study intervention arms) will review the tumor assessment data as central reading for PFS and ORR analyses for the main study phase.

Disclosure Statement: This is a Parallel, Treatment study with 2 Arms that are unblinded for previously treated metastatic nonsquamous non–small-cell lung cancer.

Number of participants:

Approximately 450 randomized patients (225 in each arm) would be adequate to achieve the targeted number of events for both PFS and OS. Assuming an accrual rate as detailed in Section 9.2, cut-off dates for final analysis of PFS and final analysis of OS will be approximately 40 and 58 months after first patient in (FPI) respectively.

Approximately 3534 patients will be prescreened for CEACAM5 status, of whom 530 patients will be screened to achieve 450 randomized patients with estimated failure rates of 85% for prescreening and 15% for screening.

Intervention groups and duration:

The duration of the study for a participant will include a period for screening of up to 28 days. Once successfully screened, participants may receive study intervention until disease progression, unacceptable AE, participant’s or investigator's decision to stop the treatment. After discontinuing study intervention, participants will return to the study site approximately 30 days (±5 days) after the last investigational medicinal product (IMP) administration or before the participant receives another anticancer therapy, whichever is earlier, for end-of-treatment assessments. For a participant who has progressive disease who does not enter the crossover treatment phase, follow-up visits will be performed every 12 weeks until the OS cut-off date or death (whichever comes first). A participant who stops treatment before documented progressive disease (achieving SD, CR, PR) should undergo a tumor assessment and a follow-up visit every 8 weeks until radiological disease progression, death, final study cut-off (OS cut-off date), or withdrawal of participant’s consent, whichever comes first. Participants who enter the crossover phase to receive tusamitamab ravtansine treatment after radiological progression should come to the site every 2 weeks for treatment and to be followed for safety.

The expected duration of study intervention for participants who benefit from study intervention may vary, based on progression date; but median expected duration of study per participant is estimated as median 9 months in docetaxel arm (1 month for screening, 4 months for treatment, and 4 months for the EOT and follow-up visits) and 12.5 months in the tusamitamab ravtansine arm (1 month for screening, 6.5 months for treatment, and 5 months for end of treatment follow-up).

If a participant is treated (including in the crossover treatment phase) and continues to benefit from treatment after the OS analysis cut-off date, the participant may continue until unacceptable toxicity, progression, participant's request to stop treatment, or Investigator decision, whichever occurs first. For cycles completed after the OS cut-off date, all ongoing SAEs (related or not), all related nonserious AEs ongoing at the cut-off date, and all new related AEs (serious or not) occurring post-cut-off date and associated concomitant medication, as well as IMP administrations and reason for EOT will continue to be collected. A safety follow-up visit will be performed approximately 30 (±5) days from last dose of tusamitamab ravtansine, even after study cut-off dates. In the case that an expanded access program is initiated, participants continuing tusamitamab ravtansine treatment at the OS cut-off date may be switched to this access program, depending on program details.

Study intervention(s)

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 clear glass vials fitted with a white plastic flip-off cap.
- Route(s) of administration: intravenous (IV) infusion
- Dose regimen: tusamitamab ravtansine will be administered on Day 1 as 100 mg/m^2 given via 1 hour 30 min IV infusion and repeated every 2 weeks. Each administration will be preceded of a pre-medication to prevent hypersensitivity reactions. The duration of one cycle will be 14 days (1 administration of tusamitamab ravtansine per cycle).

Docetaxel:

- Formulation: docetaxel is supplied as a 4 mL extractable volume of concentrate for solution for infusion of 80 mg contained in a 7 mL clear colorless glass vial with a magenta plastic flip-off cap.
- Route(s) of administration: IV infusion
- Dose regimen: Docetaxel will be administered on Day 1 as 75 mg/m² given via 1 hour IV infusion and repeated every 3 weeks. Each administration will be preceded of a premedication (as per the approved product label) to prevent hypersensitivity reaction. The duration of one cycle will be 21 days (1 administration of docetaxel per cycle).

Non-investigational medicinal product(s)

Premedication:

Both tusamitamab ravtansine and docetaxel have a potential risk of an infusion related allergic reaction and premedication should be used as detailed in Section 6.

Statistical considerations:

- **Sample size calculations:** The sample-size calculation incorporates multiplicity adjustment for the analyses of the multiple primary efficacy endpoints: progression free survival and overall survival.
- Multiplicity of primary endpoints to calculate the sample size is taken into account using Bonferroni adjustment with different weights assigned to endpoints: PFS is tested at the 1-sided 0.01 level and OS is tested at the 1-sided 0.015 level for a strong control of the overall type-I error at the 2.5% level. The graphical method of Maurer and Bretz will be applied to provide a strong type-I error control for multiple hypotheses.
  - Overall Survival: Assuming proportional hazards, a total of 363 death events will be needed to detect a hazard ratio of 0.72 using a log-rank test at the 1-sided 0.015 level with an 81% power, or at the 1-sided 0.0249 level with approximately 86% power. Based on an anticipated median OS time of 9 months in the docetaxel arm, this is expected to correspond to a median OS of 12.5 months in the tusamitamab ravtansine arm. The sample size calculation takes into account a first IA on OS for futility and efficacy when approximately 58% of OS events (approximately 210 deaths) will be observed; and a second IA on OS for efficacy when approximately 80% of events (approximately 290 deaths) will be observed.
  - Progression Free Survival: Assuming proportional hazards, a total of 221 PFS events would be needed to detect a hazard ratio of 0.615 using a log rank test at the 1-sided 0.01 level with a 90% power or at the 1-sided α-level of 0.02485 with approximately 95% power. Based on an anticipated median PFS time of 4 months in the docetaxel arm, this is expected to correspond to a median PFS of 6.5 months in the tusamitamab ravtansine arm.
  - A maximum of 450 randomized participants (225 in each arm) would be adequate to achieve the targeted number of events for both PFS and OS. The cut-off dates for final analyses of PFS and OS are predicted to be ~ 40 months for PFS and ~58 months for OS respectively after FPI. These cutoffs assume a probability of dropout (censoring reason other than cut-off reached) of 17% at 4 months for the final analysis of PFS, and a probability of dropout of 3% at 58 months for the final analysis of OS.
- **Main analysis populations:**
  - Intent-to-treat (ITT) population: this population will include all participants who have given their informed consent and who have had a treatment kit number allocated and recorded in the IRT. This population is the primary population for all efficacy parameters. All analyses using this population will be based on the treatment assigned at randomization.
  - Safety population: this population will include all participants randomly assigned to study intervention and who have received at least 1 dose of study intervention. Participants will be analyzed according to the treatment arm they received. This population is the primary population for the analysis of all safety parameters.
  - Pharmacokinetic population: this population will include safety participants who have received at least 1 dose or a part of a dose of tusamitamab ravtansine with at least

1 concentration postbaseline with adequate documentation of dosing and sampling dates and times.

- Immunogenicity population: this population will include safety participants who have received at least 1 dose or a part of a dose of tusamitamab ravtansine with at least 1 evaluable ATA result postbaseline.

- **Analysis of primary efficacy endpoints:**
  - PFS in the tusamitamab ravtansine arm will be compared to the docetaxel arm using the log-rank test procedure stratified by stratification factors as entered in the IRT. See Section 9.6 for details about the type-I error level to be used for statistical testing.
  - The estimates of the hazard ratio and corresponding 95% and α-adjusted 2-sided confidence intervals (CIs) will be provided using the Cox proportional hazard model stratified by stratification factors as entered in the IRT. The median PFS and probabilities of being progression free at different time points calculated using the Kaplan-Meier methods as well as corresponding CI will be presented by treatment arm. The Kaplan-Meier PFS curves will also be provided.
  - The cut-off date for final analysis of PFS will be the date when approximately 221 PFS events or approximately 210 deaths are observed, whichever comes first.
  - OS in the tusamitamab ravtansine arm will be compared to the docetaxel arm using the log-rank test procedure stratified by stratification factors as entered in the IRT. See Section 9.6 for details about the type I error to be used for statistical testing.
  - The estimates of the hazard ratio and corresponding 95% and α-adjusted 2-sided CI will be provided using the Cox proportional hazard model stratified by stratification factors as entered in the IRT. The median OS and probabilities of being alive at different time points calculated using the Kaplan-Meier methods as well as corresponding CI will be presented by treatment arm. Kaplan-Meier OS curves will also be provided.
  - The final OS analysis (based on approximately 363 deaths) is expected to be performed approximately 18 months after the final PFS/58% IA-OS analysis cut-off date.
- **Analysis of secondary efficacy endpoint:**
  - Objective response rate (ORR) will be summarized using descriptive statistics and 95% CIs. The ORR will be compared between treatment groups using the Cochran-Mantel-Haenszel stratified method at the significance level defined in the multiplicity section in Section 9.6.
  - Time to deterioration (TTD) in disease-related symptoms (as determined by EORTC-QLQ-LC13) in the SAR408701 arm will be compared to the docetaxel arm using the log-rank test procedure stratified by stratification factors as entered in the IRT at the significance level defined in the multiplicity section in Section 9.6.
  - The estimates of the hazard ratio and corresponding CI will be provided using the Cox proportional hazard model stratified by stratification factors as entered in the IRT. The median TTD and corresponding 95% CI will be presented by treatment arm. The

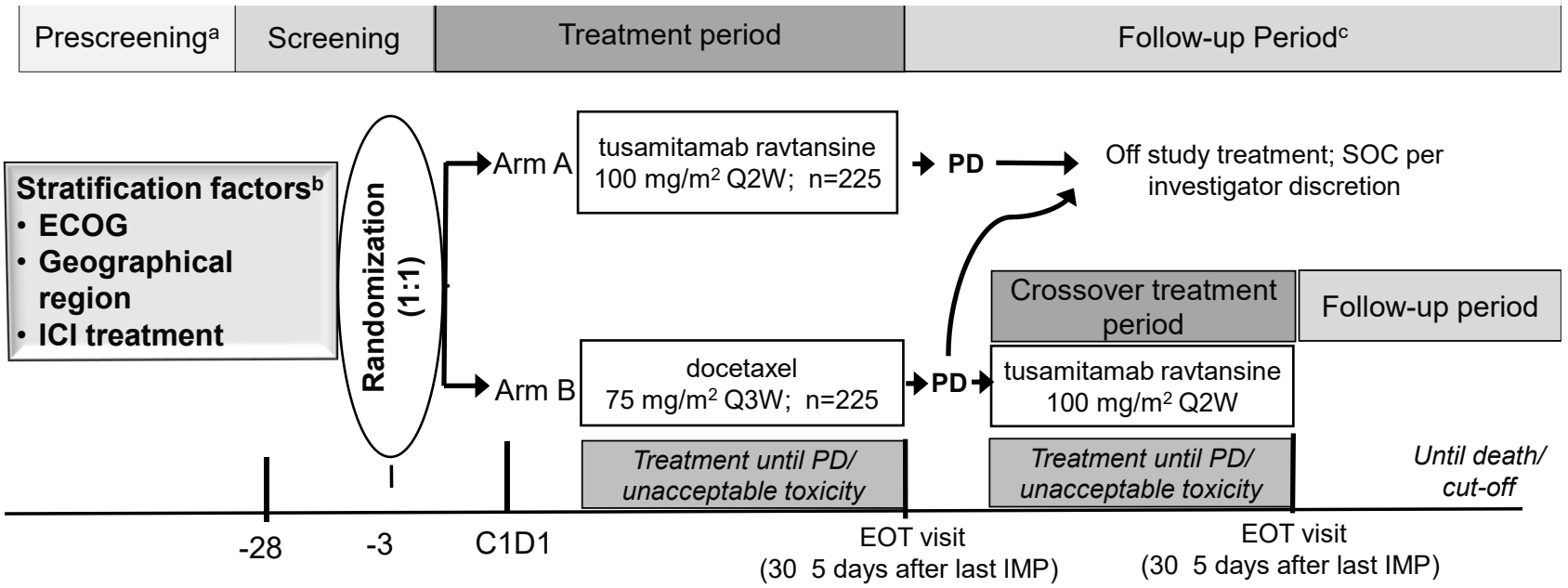
Kaplan-Meier time to deterioration in disease-related symptoms curves will also be provided.

- Same analyses will be provided for the TTD in physical function and for the TTD in role function (as determined by EORTC-QLQ-C30).
- Details of subscales from EORTC QLQ-LC13 and EORTC QLQ-C30 and list of items to be used for disease-related symptoms, physical function and role function will be provided in the statistical analyses plan.
- The duration of response (DOR) will only be summarized on the subgroup of participants who have achieved objective response. DOR for the 2 treatment arms will be summarized using Kaplan-Meier methods and displayed graphically, if appropriate. The median DOR and associated 95% CI will be provided.

- **Analysis of safety endpoints:**
  - Number (%) of patients experiencing treatment-emergent adverse events (TEAEs) and SAEs by primary system organ class and preferred term will be summarized by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0 (all grades and Grade ≥3) for the safety population. The same table will be prepared for drug-related TEAEs, TEAEs leading to treatment discontinuation, TEAEs leading to dose modification, serious TEAEs, and TEAEs with fatal outcome. For patients with multiple occurrences of the same AE within the on-treatment period, the worst grade will be used.
  - Hematology and blood chemistry results will be graded according to the CTCAE v5.0, when applicable. Number (%) of patients with laboratory abnormalities (ie, all grades and Grade ≥3) using the worst grade during the on-treatment period will be provided for the safety population.
  - Immunogenicity: incidence of anti-therapeutic antibodies will be provided for the immunogenicity-evaluable population.
- **Interim Analysis**
  - The cut-off date for the final analysis of PFS and the first IA for assessment of efficacy and futility on OS will occur when approximately 221 PFS events or approximately 58% of the targeted number of deaths (ie, approximately 210 deaths) will be available, whichever comes first.
  - The second IA for efficacy assessment on OS will occur when 80% of the targeted number of deaths are available (ie, approximately 290 deaths).
  - Control of the type I error will be ensured using an O'Brien and Fleming spending function for type I error. The nonbinding futility assessments will be based on the observed OS HR using a Cox proportional-hazard model stratified by the stratification factors. A user-defined α-spending function will also be applied on type I error for key secondary endpoints (ORR, HRQOL TTD). See Section 9.6 for further details.

Data Monitoring Committee: Yes

1.2 SCHEMA



a. Patients' tumor tissue (Archival or if not available as new fresh biopsy) will be analyzed for CEACAM5 expression, and only participants with tumors showing CEACAM5 expression level of 2+ intensity in 50% of tumor cells will be screened. Patients who have additional tumor tissue samples available during the prescreening phase may be re-assessed for CEACAM5 expression level; the most recent tissue sample assessed for CEACAM5 expression will be used to determine eligibility of participants for screening.

b. Stratification factors: ECOG (Eastern Cooperative Oncology Group) 0 vs 1; Geographical Region (Asia vs Western Europe+Australia+NA vs ROW); prior ICI (immune checkpoint inhibitors) treatment: Sequential versus combination with chemotherapy

c. A participant discontinuing main study treatment due to a reason other than PD will be followed every 8 weeks until documented disease progression. After disease progression, the participant may be treated with SOC or, if treated under docetaxel arm and if the crossover phase is implemented, tusamitamab ravtansine, per investigator discretion.

Abbreviations: C1D1=treatment Cycle 1 Day 1; ECOG=Eastern Cooperative Oncology Group; EOT=End of Treatment; ICI=immune checkpoint inhibitor; IMP=investigational medicinal product; NA=North America; PD=progressive disease; Q2W=every 2 weeks; Q3W=every 3 weeks; ROW=rest of world.

1.3 SCHEDULE OF ACTIVITIES (SOA)

1.3.1 Main study phase

Procedure	Pre-screening[a]	Screening[b]	Treatment cycle 1			Treatment Cycle 2 and subsequent		End of treatment (Day 30 ±5 days after last infusion)	Follow-up period[d]	Notes
Day		Days prior to initial infusion	D1		D3 (24-72 h after Infusion)					
			Pre-infusion[c]	EOI		Pre-infusion[c]	Every 8 weeks			
CEACAM5 expression status[a] (archival or fresh tumor tissue) – central IHC/ prescreening Informed consent	X									See Section 8.8.1
Informed Consent		X								
Inclusion/exclusion criteria		≤28	X							See Section 5.1 and Section 5.2
Demography and medical/surgical/disease history/smoking history	X	≤28								See Section 8
PS, VS, Body Weight/Height		≤7	X			X			PS only (if on-site visit)	See Section 8.2.1 and Section 8.2.3. Height only at Screening visit, before the IRT call.
Physical examination/ signs and symptoms		≤7	X			X		X	X	See Section 8.2.1
Hematology		≤7	X			X		X		See Section 8.2.5 and Appendix 2 Section 10.2
Coagulation		≤7	X			X		X		See Section 8.2.5 and Appendix 2 in Section 10.2

Procedure	Pre-screening[a]	Screening[b]	Treatment cycle 1			Treatment Cycle 2 and subsequent		End of treatment (Day 30 ±5 days after last infusion)	Follow-up period[d]	Notes
Day		Days prior to initial infusion	D1		D3 (24-72 h after Infusion)					
			Pre-infusion[c]	EOI		Pre-infusion[c]	Every 8 weeks			
Blood chemistry		≤7	X			X		X		See Section 8.2.5 and Appendix 2 in Section 10.2
Troponin		≤7				X		X		During study treatment: for SAR408701 arm: at end of Cycle 4 for Docetaxel arm: at end of Cycle 3
HBV & HCV serology and HIV test (only if required at country level)		X								See Appendix 2 in Section 10.2
Serum pregnancy test		≤7				X		X		Mandatory serum test at screening and EOT and if required per local regulations, serum/ urine test during study treatment period. See Appendix 2 in Section 10.2
12-lead ECG		≤7	X	X		X		X		See Section 8.2.4
Specific ocular tests		≤28						X		EOT ocular assessment required only for ongoing corneal event or ocular symptoms at EOT visit. See Section 8.2.2

Procedure	Pre-screening[a]	Screening[b]	Treatment cycle 1			Treatment Cycle 2 and subsequent		End of treatment (Day 30 ±5 days after last infusion)	Follow-up period[d]	Notes
Day		**Days prior to initial infusion**	**D1**		**D3** (24-72 h after Infusion)					
			Pre-infusion[c]	**EOI**		**Pre-infusion[c]**	**Every 8 weeks**			
Tusamitamab ravtansine/Docetaxel administration			X			X				See Section 6.1
AE assessment	X	X	Continuously throughout the study period							See Section 8.2, Section 8.3, Section 10.3
Concomitant medication		X	Continuously throughout the study period							See Section 6.5
Tumor assessment		≤28					X	X	X	See Section 8.1
ePRO (EORTC QLQ-C30 and EORTC-LC13)[e]			X[e]			X		X	X	See Section 8.11
Plasma for tumor cfDNA and whole blood for germline DNA			X							See Section 8.7
Circulating CEA		≤28					X	X	X	See Section 8.6.1
Further anticancer therapy[f]									X	
Survival status									X	Assessed every 12 weeks See Section 7.1.1
Tusamitamab ravtansine pharmacokinetics			X	X	X	X----------X				See Section 8.5
Tusamitamab ravtansine immunogenicity			X----------X							See Section 8.9

a **Prescreening:**A prescreening-Informed Consent will be signed by the patient for this purpose. For analyses of CEACAM5 expression. Limited patient & diseases characteristics will be collected in patients who are not eligible for screening; ie, CEACAM5 negative or CEACAM5 positivity below the threshold value: gender, race, ethnicity, smoking status, age, histology and stage at diagnosis and biomarkers when available (tumor mutation status [eg, *EGFR, ALK, ROS, MET, RET, BRAF]*, PD-L1 and circulating CEA value)

b **Screening:** Informed consent should be signed before any study specific procedures. It can be signed more than 28 days prior to randomization. Screening time indicates the timeframe relative to first IMP administration in which exams used to support eligibility have to be done prior to randomization. All the tests or procedures on D1 should be done at predose time unless otherwise stated. Assessments must be performed prior to first IMP administration: patients 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 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 randomization.

c **D1 predose**: Cycle 1 D1 refers to the day the patient receives the initial dose of IMP. D1 of Cycle 2 and of each subsequent cycle corresponds to D15 if patient allocated to tusamitamab ravtansine pharmacokinetics (respectively to D22 if allocated to Docetaxel arm) of the previous cycle. During treatment, D1 assessment can be done on the day of infusion (before infusion) or the day before. C1D1 hematology, blood chemistry and coagulation tests may be omitted if baseline test performed within 7 days are normal. If baseline tests are abnormal should be repeated within 2 days of first study intervention.

d **Follow-up period:** during the follow-up period, SAEs (regardless of relationship with study treatment) and IMP-related AEs ongoing at the end of study treatment, and any new IMP-related AE/SAE/AESI will be followed until resolution or stabilization (stabilization is defined as an event ongoing without any change for at least 3 months). Date of disease progression and further anticancer treatment will be collected at the follow-up visits. Patients who stopped treatment before documented progressive disease (achieving stable disease, complete or partial response) should undergo a tumor assessment and a follow-up visit every 8 weeks until radiological disease progression, death, OS cut-off date, or withdrawal of patient's consent, whichever comes first. Patients with documented disease progression should attend a follow-up visit every 12 weeks until OS study cut-off date or death (whichever comes first). For participants who progress on docetaxel and cross over to receive tusamitamab ravtansine treatment, refer to schedule in Section 1.3.2).

e ePRO to be completed at site visit prior to any tests/medications and prior to any discussion of health status with healthcare personnel at the site. C1D1 assessment can be done up to -3 days, just after randomization call. The estimated time to complete the EORTC QLQ-C30 and the EORTC QLQ LC13 is approximately 10 to 15 minutes

f Participants enrolled to tusamitamab ravtansine can be treated with local standard of care per investigator discretion. Participants enrolled to the doxetaxel arm can be treated either with local standard of care or, if the crossover phase is implemented, with tusamitamab ravtansine, per investigator discretion. Eligibility for crossover treatment is detailed in Section 5, and related study procedure and safety follow-up requirements are detailed in Section 1.3.2.

1.3.2 Crossover phase *(if implemented)*

Procedure	Assessment[a]	C1c[b] and subsequent cycles	End of treatment- crossover	Follow-up period[c]	Notes
		Day 1	(30 ±5 days after last infusion)		
Day	**Days before initial infusion**				
Informed Consent	X				
Eligibility for crossover	≤7				See Section 5.1 and Section 5.2
PS, VS, Body Weight	≤7	X		Only PS if on-site visit	See Section 8.2.1 and Section 8.2.3.
Physical examination/signs + symptoms	≤7	X	X		See Section 8.2.1
Hematology	≤7	X	X		See Section 8.2.5 and Appendix 2 Section 10.2
Coagulation	≤7	X	X		See Section 8.2.5 and Appendix 2 in Section 10.2
Blood chemistry	≤7	X	X		See Section 8.2.5 and Appendix 2 in Section 10.2
Troponin	≤7	X[d]	X[d]		
Serum pregnancy test	≤7		X		Mandatory serum test before the start of tusamitamab ravtansine crossover treatment and EOT, and as required per local regulations; serum/urine test during study treatment period. See Appendix 2 in Section 10.2.
12-lead ECG	≤7	X	X		Before administration at each cycle for first 4 cycles, and then every other cycle
Specific ocular tests	≤7		X		Mandatory before start of crossover treatment, whenever ocular symptoms are observed, and at EOT. (Section 8.2.2.)
Tusamitamab ravtansine administration		X			See Section 6.1
AE assessment		Continues throughout treatment from first dose up to 30 days after last dose			See Section 8.2, Section 8.3, Section 10.3
Concomitant medication		Continues throughout treatment from first dose up to 30 days after last dose			See Section 6.5
Circulating CEA	≤28	X	X	X	See Section 8.6.1
Further anticancer therapy				X	
Survival status				X	Assessed every 12 weeks; see Section 7.1.1

Abbreviations: AE=adverse event; C=cycle; c=crossover; CEA=carcinoembryonic antigen; ECG=electrocardiogram

a If within the specified window before first crossover infusion, assessments at the EOT visit can be used as pre-assessment before starting the crossover treatment.

b Cycle 1 assessment can be omitted if pre-assessment values are either normal, or abnormal values within eligibility for crossover treatment and considered by the investigator as not clinically significant.

c A participant who discontinues crossover treatment due to PD should be followed every 12 weeks for survival status.

d Troponin will be measured before the first dose of the crossover phase, after the end of Cycle 4-crossover (before administration of tusamitamab ravtansine at the Cycle 5-crossover visit), and at the End of Treatment-crossover visit (see Section 8.2.5).

2 INTRODUCTION

Tusamitamab ravtansine (SAR408701) is an antibody-drug conjugate (ADC) combining hu769_4D4 (SAR408377), a humanized antibody that recognizes selectively the A3-B3 extracellular domain of CEACAM5, a tumor-associated carcinoembryonic antigen, with the potent cytotoxic maytansinoid derivative, DM4, that inhibits microtubule assembly. Tusamitamab ravtansine is expected to selectively deliver DM4 to cancer cells expressing the CEACAM5 antigen, such as colon, stomach, and its signet-ring cell subtype, as well as nonsquamous NSCLC.

Carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5) was first described in 1965 as a tumor-associated antigen in human colon cancer tissue extracts (1). High levels of CEACAM5 expression have since been observed in several epithelial tumors while in normal adult tissue, its expression is limited to few tissues (2, 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, the stomach and its subtype signet-ring cell, as well as in nonsquamous NSCLC.

2.1 STUDY RATIONALE

Despite recent progress in the treatment of advanced NSCLC, there remains a need for effective new treatment at the time of disease progression. Tusamitamab ravtansine, an antibody conjugate to the cytotoxic (DM4), is expected to selectively deliver DM4 to cancer cells expressing the CEACAM5 and thus could bring a clinical benefit and improved safety profile over the existing chemotherapy option.

In first in human study TED13751, a cohort of patients with heavily pretreated nonsquamous NSCLC with tumor cell membranes shown to be CEACAM5 positive (≥2+ in intensity in 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. Results from the first 32 patients treated showed encouraging antitumor activity associated with a response rate of 25% (90% confidence interval [CI]: 14.70% to 39.20%; 4); this cohort was expanded to include a total of 64 high CEACAM5 expressers and 28 moderate expressers. Of the high expressers, 13 participants had PR (ORR, 20.3%); an additional 28 patients (43.8%) had SD as BOR.

Data from 11 patients (9 high expressers and 2 moderate expressers) treated long term (ie, ≥12 months of tusamitamab ravtansine treatment) showed that 7 patients (64%) had a confirmed PR, and 4 (36%) had SD as best overall response (5). Almost half of (7 of 15) patients with nonsquamous NSCLC who achieved a confirmed PR maintained the response after 1 year of treatment, suggesting that response to tusamitamab ravtansine in heavily pretreated patients was durable and frequently sustained. No new or unexpected safety signals were observed; none of these patients on long-term treatment discontinued the treatment because of drug-related AEs, and corneal AEs were manageable with dose modification.

2.2 BACKGROUND

Lung cancer is one of the most commonly diagnosed cancers and is the leading cause of cancer-related mortality worldwide (6). Non-small-cell lung cancer (NSCLC) accounts for 80% to 85% of all lung cancers and is composed of several histopathological subtypes, the most common of which are adenocarcinoma (40% to 60%) and squamous-cell carcinoma (10% to 15%).

The majority of patients with NSCLC present at an advanced stage at the time of diagnosis. These patients have a median overall survival (OS) of up to 8 to 12 months and a 5 year survival rate of approximately 18% (6, 7). About 15%-20% of patients with NSCLC have key genomic alterations such as epidermal growth factor receptor gene (*EGFR*) mutations and *ROS1* and anaplastic lymphoma kinase (*ALK*) rearrangements that are amenable to targeted therapy.
Until recently the only available treatment option, for advanced or metastatic nonsquamous NSCLC that lacks targetable mutations, was chemotherapy. Systemic therapy with platinum-based doublet regimens, with or without maintenance therapy, is the current first-line treatment for patients with advanced NSCLC (8). The addition of bevacizumab a monoclonal antibody against vascular endothelial growth factor (VEGF) or necitumumab an antibody that targets EGFR produced modest improvement in survival (9, 10). In second line treatment the standard of care has been docetaxel (11).

More recently immunotherapy has become a new paradigm for the treatment of NSCLC. In particular, monoclonal antibodies targeting the programmed death-1 receptor (PD-1)/PD ligand 1 (PD-L1) pathway and have emerged as powerful new therapeutic tools in several clinical trials. Three drugs targeting the PD-1 pathway (nivolumab, pembrolizumab and atezolizumab) have been approved for the treatment of both chemotherapy-naïve and previously treated advanced stage NSCLC (12, 13, 14, 15), however only small subset of patients (20%-30%) respond to treatment. Despite recent improvement of outcome following initial therapy lines, including the new antibodies anti PD-1/PD-L1, the disease often progresses.

In this situation, the main therapeutic options remain docetaxel, however its efficacy is modest and offset by substantial toxic effects (12, 13, 14). Therefore, newer therapeutic approaches are needed to improve the clinical efficacy and health-related quality of life (HRQOL) in patients with advanced NSCLC.

2.3 BENEFIT/RISK ASSESSMENT

Based on the available data, the main risk observed during clinical development is corneal toxicity presenting as microcystic keratopathy, which is reversible and manageable with dose delay and dose reduction in some patients. Peripheral neuropathy is identified risk in patients that have been previously exposed to neurotoxic drugs. Other potential risks include gastro-intestinal toxicity, bone marrow toxicity, liver enzyme increased, cardiotoxicity, as well as hypersensitivity (infusion) reactions for tusamitamab ravtansine. Based on the current data on efficacy and safety obtained in the ongoing studies of tusamitamab ravtansine (TED13751 and TCD15054) supports its continued clinical development. More detailed information about the known and expected benefits and risks and reasonably expected adverse events of tusamitamab ravtansine may be found in the Investigator's Brochure.

3 OBJECTIVES AND ENDPOINTS

Table 1 - Objectives and endpoints

Objectives	Endpoints
Primary	
Study is designed with 2 primary endpoints that will be analyzed on randomized participants at the time of the cut-off date for each given analysis (progression free survival [PFS] and overall survival [OS]). Study success is defined either on PFS or OS • The primary objective is to determine whether tusamitamab ravtansine improves the progression free survival (PFS) when compared to docetaxel in participants with metastatic nonsquamous NSCLC expressing CEACAM5 ≥2+ in intensity in at least 50% of the tumor cell population and previously treated with standard-of-care platinum-based chemotherapy and an immune checkpoint inhibitor (ICI)	• The primary endpoint is PFS as assessed by independent blinded review committee (IRC) and based on RECIST 1.1 assessments. PFS will be defined as the time from randomization to the date of the first documented disease progression or death due to any cause, whichever comes first.
• The primary objective is to determine whether tusamitamab ravtansine improves the overall survival (OS) when compared with docetaxel in participants with metastatic nonsquamous NSCLC expressing CEACAM5 ≥2+ in intensity in at least 50% of the tumor cell population and previously treated with standard-of-care platinum-based chemotherapy and an immune checkpoint inhibitor.	• The primary endpoint is OS and defined as the time from randomization to the date of death due to any cause.
Secondary	
• To compare the objective response rate (ORR) to tusamitamab ravtansine with docetaxel	• Objective response rate will be defined as the proportion of participants who have a complete response (CR) or partial response (PR), as best overall response derived from Overall Response (OR) determined by the IRC per RECIST 1.1
• To compare the health-related quality of life (HRQOL) with tusamitamab ravtansine with docetaxel	• HRQOL will be analyzed through three different endpoints: • Time to deterioration (TTD) in disease related symptoms (composite endpoint of cough, chest pain and dyspnea) as determined by EORTC QLQ-LC13 • TTD in physical function as determined by EORTC QLQ C-30 • TDD in role function as determined by EORTC QLQ C30 The TTD is defined as the time from baseline (Cycle 1, Day 1) until the first ≥10-point change from baseline up to the End-of-Treatment assessment

Objectives	Endpoints
• To evaluate the safety of tusamitamab ravtansine compared to docetaxel	• Incidence of TEAEs and SAEs and laboratory abnormalities according to NCI CTCAE v5.0
• To assess the duration of response (DOR) to tusamitamab ravtansine as compared with docetaxel	• Duration of response (DOR) is defined as the time from first documented evidence of CR or PR until progressive disease (PD) determined per RECIST 1.1 or death from any cause, whichever occurs first
Tertiary/exploratory	
• To characterize the pharmacokinetic (PK) of tusamitamab ravtansine	• Plasma concentrations of tusamitamab ravtansine during the treatment period
• To assess the potential immunogenicity of tusamitamab ravtansine	• Incidence of anti-therapeutic antibodies (ATAs) against tusamitamab ravtansine
• To assess the relationship between the tumor mutation profiles detected in the circulating free DNA (cfDNA) at baseline with efficacy outcome	• Plasma analysis for tumor cfDNA at baseline
• To explore modulations of circulating CEA as a potential pharmacodynamics biomarker of response to tusamitamab ravtansine treatment	• Circulating CEA at baseline and during the treatment period
• To explore PK and pharmacodynamics (PD) (PK/PD) relationship	• Exploration of relationship between relevant safety and efficacy endpoints with PK parameters during treatment period
• To identify disease and patient characteristics that could be associated to CEACAM5 expression	• To evaluate disease and patient characteristics in each CEACAM5 expression group (CEACAM5 positive ≥50%; CEACAM5 positive 1% to <50%; and CEACAM5 negative) and CEACAM5 expression patterns
Tertiary endpoints associated with the crossover population:	
• To assess safety of tusamitamab ravtansine in terms of TEAEs, SAEs, and treatment-related AEs in participants previously treated with docetaxel	• Incidence of TEAEs, SAEs, treatment-related AEs, and laboratory abnormalities according to NCI CTCAE v5.0 in the crossover treatment phase
• To assess tusamitamab ravtansine efficacy in terms of ORR in participants receiving crossover tusamitamab ravtansine treatment after documented disease progression on docetaxel	• Objective response rate in the crossover treatment phase, defined as the proportion of participants who have a complete response (CR) or partial response (PR), as best overall response reported by the investigator per RECIST 1.1

3.1 APPROPRIATENESS OF MEASUREMENTS

Each of the efficacy, safety and QoL assessments chosen for use in this study is 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 3, randomized, open-label, multicenter study comparing tusamitamab ravtansine 100 mg/m² (Arm A) and docetaxel 75 mg/m² (Arm B) in patients with metastatic nonsquamous - NSCLC expressing CEACAM5 and previously treated with platinum-based chemotherapy and an immune checkpoint inhibitor.

To identify nonsquamous NSCLC patients with CEACAM5 positive tumors, there is a prescreening phase to perform prospective analyses of CEACAM5 expression on the most recent archival tumor tissue. An in vitro diagnostic medical device manufactured for Sanofi is provided by a third party. This in vitro diagnostic medical device is a qualitative immunohistochemical assay under performance evaluation, called CEACAM5 IHC 769 assay. For this analysis, at least 5 × 4 µm slides from FFPE archival tissue should be sent to the central laboratory designated by the Sponsor. If less material is available, a participant could be eligible only after discussion with the Sponsor, who will confirm that there may be sufficient material for key CEACAM5 expression analyses. In case of unavailable archival tissue, a fresh biopsy can be considered in participants who have reachable lesion that is suitable for biopsy. This prescreening activity can be performed in advance, when participant may be on prior anticancer therapy due to the progression of their underlying disease condition.

Screening visit should be performed in patient whose tumor tissue analyses at central laboratory meets the CEACAM5 expression of ≥2+ in intensity involving ≥50% of the tumor cell population.

The study will have 3 main periods: screening, treatment and follow up. After being screened the eligible patients will be randomized (1:1) to one of the following treatment arms:

- Treatment A: tusamitamab ravtansine (SAR408701) every 2 weeks (Q2W cycle) at the dose of 100 mg/m^2.
- Treatment B: Docetaxel every 3 weeks (Q3W cycle) at the dose of 75 mg/m^2.

Treatment allocation will be performed by an Interactive Response Technology (IRT). All eligible patients will be randomly assigned to either of the experimental arm or the control arm in a 1:1 proportion. Allocation to the 2 treatment arms will be done using stratified randomization based on Eastern Cooperative Oncology Group (ECOG) performance status (0 versus 1), previous ICI treatment (sequential versus combination with chemotherapy) and geographical region (Asia versus Western Europe + Australia + North America versus Rest of the World [RoW]).

4.1.1 Duration of the study period

The duration of the study for a participant prescreened and CEACAM5 positive will include a period for screening of up to 28 days. The cycle duration is 14 days for tusamitamab ravtansine and 21 days for docetaxel therapy.

The expected treatment period for participants who benefit from study intervention may vary, based on progression date.

After discontinuation of study intervention, participants will return to the study site approximately 30 days (±5 days) (for end-of-treatment [EOT] assessments) after the last IMP administration or before the start of another anticancer therapy, whichever is earlier.

After the EOT visit, during the FU visits, the participants will be monitored for all ongoing related AEs and regardless of relationship all the SAEs and adverse event of special interest (AESIs) until resolution or stabilization (ie, an event ongoing without any change for at least 3 months).

All new related AEs, SAEs, or Events of Special Interest, including deaths will be followed until resolution or stabilization.

For participants who have progressive disease, follow up visits will be performed every 12 weeks until OS study cut-off date or death (whichever comes first), unless the participant is allocated to crossover tusamimatab ravtansine treatment. In addition, if the participant discontinues study intervention for reasons other than progression, the participant should undergo a tumor assessment and a follow-up visit every 8 weeks until radiological disease progression, death, final study cut-off (OS cut-off date), or withdrawal of participant's consent, whichever comes first.

The total estimated duration of enrollment will be approximately 50 months. The expected duration of treatment for participants who benefit from study intervention may vary, based on progression date; but median expected duration of study per participant is estimated as median 9 months in docetaxel arm (1 month for screening, 4 months for treatment, and 4 months for the EOT and follow-up visits) and 12.5 months in the tusamitamab ravtansine arm (1 month for screening, 6.5 months for treatment, and 5 months for EOT follow-up), excluding any potential impact of the crossover phase.

4.1.2 Crossover treatment phase (if implemented)

Crossover to tusamitamab ravtansine treatment may be implemented by the Sponsor for participants randomized to docetaxel upon progression, in the case that:

- the final PFS outcome is statistically significant, and
- statistical power for final analysis of the primary endpoint of OS is expected to not be significantly altered

The decision to implement the crossover phase will be communicated to sites by the Sponsor in writing after the final analysis of PFS/IA of OS at 58% IF. The decision for each participant to receive crossover treatment with tusamitamab ravtansine will be based on the Investigator's discretion after documented PD per RECIST 1.1 as assessed by the Investigator and confirmed by the Sponsor after review of the eCRF data.

Intolerance to chemotherapy, withdrawal of consent, or clinical progression without documented radiological progression per RECIST 1.1 is not sufficient for eligibility for crossover to tusamitamab ravtansine. Participants allocated to crossover tusamitamab ravtansine treatment will

come to the clinic every 2 weeks for treatment and follow-up procedures as detailed in Section 1.3.2.

Treatment with tusamitamab ravtansine during the crossover phase will continue until disease progression, unacceptable AEs, participant's decision to discontinue the study, or Investigator discretion, whichever occurs first. An EOT visit will be performed 30 (±5) days after the last crossover dose for safety follow-up.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Lung cancer is the leading cause of death and only 18% of all lung cancer patients are alive 5 years or more after initial diagnosis. Based on histology, therapy and prognosis, lung cancer is divided into 2 major classes: small-cell lung cancer (SCLC) and non–small-cell lung cancer (NSCLC). NSCLC accounts 80% of lung cancer and it includes 2 major subtypes: nonsquamous carcinoma (including adenocarcinoma, large-cell carcinoma, and other subtypes) and squamous-cell (epidermoid) carcinoma. Adenocarcinoma is the most common subtype of nonsquamous NSCLC (11).

The past decade has dramatically changed the approach on diagnosis and treatment of lung cancer with the concept of personalized medicine, which led discovery of several therapeutic options that are only approved for treatment of patients with specific histopathologic characteristics (16).

Accurate pathologic assessment with tumor mutation profile and staging are essential for treatment decision. In general, systemic therapy is recommended for patients with metastatic (stage IV) disease, especially with disseminated metastasis. The type of systemic therapy depends on the histologic type, whether there are genetic alterations that can be targeted for therapy, and the performance status of the patient.

In the advanced setting, platinum-based chemotherapy was considered the gold standard, with evidence of improved survival, symptom control, and superior quality of life compared to best supportive care. After improvement of biomarker testing for genetic alterations, the number of available targeted therapies has been increasing, and targeted therapy has been shown to decrease tumor burden, decrease symptoms, and dramatically improve the quality of life for patients with specific genetic alterations.

Doublet chemotherapy regimens are recommended as first-line chemotherapy for nonsquamous NSCLC patients whose tumors are negative for *ALK* and *ROS1* re-arrangement and sensitizing *EGFR* mutations and have PD-L1 expression <50% or unknown. Based on genetic profiling, targeted therapies maybe considered as first line before, or as second line therapy after, platinum-based chemotherapy.

Immune-check point inhibitors are recommended as subsequent therapy for all patients, with reported data on improved survival, longer response duration and better safety profile when compared to chemotherapy. Current data suggest that patients with EGFR mutations or ALK rearrangement have a low response rate to PD-1 or PD-L1 inhibitors when compared with patients

without these alterations; so not considered as recommended subsequent treatment in patients with these alterations.

Docetaxel is still considered as the best control arm in patients with relapsed advanced NSCLC patients after platinum-based chemotherapy and ICI, if indicated. The Phase 3 study in subsequent therapy for NSCLC, comparing docetaxel in combination with ramucirumab versus docetaxel alone reported slightly increased overall survival (10.5 versus 9.1 months, HR 0,86, 95% CI 0.75-0.98; p<0.023), which is considered as not clinically relevant (11). Docetaxel is determined as the control arm in this study as still considered as widely used standard of care in the targeted patient population.

4.3 JUSTIFICATION FOR DOSE

In a first-in-human study (TED13751), the dose-escalation phase explored doses between 5 and 150 mg/m^2 administered in cycles once every 2 weeks, and the recommended dosage was determined as 100 mg/m^2 administered every 2 weeks. There is an ongoing cohort of heavily pretreated nonsquamous NSCLC patients with CEACAM5-positive tumors treated with tusamitamab ravtansine at the recommended dose of 100 mg/m² every 2 weeks. Preliminary results from the first 32 evaluable patients treated showed encouraging antitumor activity in heavily pretreated patients with nonsquamous NSCLC CEACAM5 ≥50% (4). This antitumor activity was associated with a response rate of 25% per RECIST 1.1 (90% CI 14.70%-39.20%) in the response-evaluable population.

4.4 END OF STUDY DEFINITION

There are 3 planned cut-off dates for the study:

The estimated first trial cut-off date, for the final analysis of PFS and 58% interim analysis of OS will be approximately 40 months after FPI

The estimated second cut-off date for 80% interim analysis of OS will be approximately 48 months after the FPI.

The estimated third cut-off date for the final analysis of OS will be approximately 58 months after FPI.

The primary analysis of OS corresponds either to the positive OS interim analysis or the final OS analysis.

Secondary efficacy endpoints will be analyzed and tested at the time of the final PFS analysis if PFS and/or 58% IA of OS is significant; if not, at the time of the 80% interim OS (if OS is statistically significant), otherwise at the time of the final analysis of OS.

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 for the last participant in the trial globally. It will occur at the final study cut-off planned at 58 months after the first participant is randomized or when all participants have had the opportunity to complete the EOT visit 30 days after the last study treatment administration (main study or crossover treatment), whichever is the

latest. In the case that an expanded access program is initiated, participants continuing tusamitamab ravtansine treatment at the OS cut-off date may be switched to this access program, depending on program details.

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 ≥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. Histologically or cytologically proven diagnosis of nonsquamous NSCLC metastatic disease at study entry; - meeting all 3 of the following criteria:

a) Having progressive disease during or after platinum-based chemotherapy (at least 2 cycles).
Maintenance therapy following platinum-based chemotherapy is not considered as a separate regimen. Adjuvant/neoadjuvant treatment for a patient who had a relapse with metastatic disease during or within 6 months of completion of treatment will be considered as first line treatment.

AND

b) Having progressive disease during or after one immune checkpoint inhibitor (anti-PD-1/PD-L1); this could be given as monotherapy or in combination with platinum-based chemotherapy (whatever the order).

AND

c) Participant with *EGFR* sensitizing mutation or *BRAF* mutation or *ALK/ROS* alterations must be able to demonstrate progression of the disease on approved treatments for these conditions, in addition to platinum-based chemotherapy and immune checkpoint inhibitor.

I 03. Participants with CEACAM5 expression of ≥2+ in intensity in archival tumor sample (or if not available fresh biopsy sample) involving at least 50% of the tumor cell population as demonstrated prospectively by a centrally assessed ICH assay. At least 5 × 4 µm slides from FFPE tumor tissue are required. If less material is available, patient could still be eligible after discussion with the Sponsor who will assess and confirm that there is sufficient relevant material for key evaluations.

I 04. At least one measurable lesion by RECIST v1.1 as determined by local site investigator /radiology assessment. Irradiated lesion can be considered measurable only if progression has been demonstrated on irradiated lesion.

I 05. Eastern Cooperative Oncology Group (ECOG) performance status 0-1.

Sex

I 06. Male or female

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

a) Male participants

Male participants: A male participant must agree to use contraception methods (see Appendix 5, Section 10.5) during the intervention period and for at least 6 months after the last dose of study intervention. Men being treated with docetaxel should be advised to seek advice on conservation of sperm prior to treatment.

b) Female participants

Female participants: A female participant is eligible to participate if she is not pregnant (see Appendix 5, Section 10.5), not breastfeeding, and at least one of the following conditions applies:

Not a woman of childbearing potential (WOCBP) as defined in Appendix 5 (Section 10.5).

OR

A WOCBP who agrees to follow the contraceptive guidance in Appendix 5 (Section 10.5) during the intervention period and for at least 7 months after the last dose of study intervention.

Informed Consent

I 07. Capable of giving signed informed consent as described in Appendix 1, Section 10.1.3, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

Inclusion criteria added with amendment 5 for eligibility for the crossover treatment phase (if implemented as detailed in Section 4.1.2):

Retesting of tumor CEACAM5 status is not required. Participants will be considered eligible for crossover tusamitamab ravtansine treatment if they meet all the following criteria.

I 801. Documented radiological progression per RECIST v1.1 as assessed by the Investigator during or after study treatment with docetaxel.

I 802. Written ICF for the crossover treatment phase is signed by the participant in compliance with the requirements and restrictions listed in the ICF and in this protocol (Appendix 1, Section 10.1.3).

I 803. At least one measurable lesion by RECIST v1.1 as determined by local site investigator/radiology assessment. An irradiated lesion can be considered measurable only if progression has been demonstrated on the irradiated lesion.

I 804. Eastern Cooperative Oncology Group (ECOG) performance status 0-1.

I 805. Contraceptive use by men or women should be consistent with local regulations regarding the methods of highly effective contraception for those participating in clinical studies.

a) Male participants

Male participants: A male participant must agree to use contraception methods (see Appendix 5, Section 10.5) during the intervention period and for at least 6 months after the last dose of study intervention. Men being treated with docetaxel should be advised to seek advice on conservation of sperm prior to treatment.

b) Female participants

Female participants: A female participant is eligible to participate if she is not pregnant (see Appendix 5, Section 10.5), not breastfeeding, and at least one of the following conditions applies:

Not a woman of childbearing potential (WOCBP) as defined in Appendix 5 (Section 10.5).

OR

A WOCBP who agrees to follow the contraceptive guidance in Appendix 5 (Section 10.5) during the intervention period and for at least 7 months after the last dose of study intervention.

5.2 EXCLUSION CRITERIA

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

Medical conditions

E 01. Untreated brain metastases or history of leptomeningeal disease. Patients with previously treated brain metastases may participate provided they are stable (ie, without evidence of progression) by imaging performed at least 4 weeks after CNS-directed treatment and at least 2 weeks prior to the first administration of study intervention, and any neurologic

symptoms have returned to baseline; and there is no evidence of new or enlarging brain metastases; and the patient does not require any systemic corticosteroids for management of brain metastases within 2 weeks prior to the first dose of study intervention.

E 02. Significant concomitant illnesses, including all severe medical conditions which, in the opinion of the investigator or Sponsor, would impair the patient's participation in the study or interpretation of the results.

E 03. 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 04. History of known acquired immunodeficiency syndrome (AIDS) related illnesses or known HIV disease requiring antiretroviral treatment, or active hepatitis A, B (defined as either positive HBs antigen or positive hepatitis B viral 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 HCV RNA results greater than the lower limits of detection of the assay) infection. HIV serology at screening will be tested only for participants enrolled in German sites and any countries where mandatory as per local requirements.

E 05. Nonresolution of any prior treatment related toxicity to < Grade 2 according to NCI CTCAE v5.0, except for alopecia, vitiligo and active thyroiditis controlled with hormonal replacement therapy.

E 06. Unresolved corneal disorders or any previous corneal disorder that considered by ophthalmologist that patient may have higher risk of drug induced keratopathy. The use of contact lenses is not permitted. Patients using contact lenses who are not willing to stop wearing them for the duration of the study intervention.

E 07. Medical conditions requiring concomitant administration of medications with narrow therapeutic window, metabolized by CYPs (See Appendix 9, Section 10.9) and for which a dose reduction cannot be considered.

E 08. 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 first administration of study intervention.

Prior/concomitant therapy

E 09. Concurrent treatment with any other anticancer therapy.

E 10. Prior treatment with docetaxel

E 11. Prior therapy targeting CEACAM5

E 12. Prior maytansinoid treatment (DM1 or DM4 antibody drug conjugate)

E 13. 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 antitumor therapy (chemotherapy, targeted agents, immunotherapy and radiotherapy, or any investigational treatment.

E 14. Any major surgery within the preceding 3 weeks of the first study intervention administration.

E 15. Contraindication to use of corticosteroid premedication

Prior/concurrent clinical study experience

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

Diagnostic assessments

E 17. Poor organ function as defined by any one of the following:

- Serum creatinine >ULN and eGFR <50 mL/min/1.73 m^2 as estimated using the aMDRD formula. Participants with elevated creatinine are eligible if eGFR ≥50 mL/min/1.73 m^2.
- Total bilirubin >1.0 × ULN.
- AST, ALT >2.5 × ULN or AST, ALT >1.5 × ULN concomitant with ALP >2.5 × ULN. ALP >5 × ULN with normal ALT/AST for patients with bone metastases.
- Neutrophils <1.5 × 10^9/L or platelet count <100 × 10^9/L or hemoglobin <9 g/dL

Other exclusions

E 18. Individuals accommodated in an institution because of regulatory or legal order; prisoners or subjects who are legally institutionalized

E 19. Any country-related specific regulation that would prevent the subject from entering the study - (country specific requirements)

E 20. 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 21. Participants who are dependent on the Sponsor or Investigator (in conjunction with Section 1.61 of the ICH-GCP Ordinance E6)

E 22. 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

E 23. Any specific situation during study implementation/course that may raise ethics considerations

E 24. Hypersensitivity to any of the study interventions, or components thereof (EDTA), or drug (paclitaxel, polysorbate 80) or other allergy that, in the opinion of the Investigator, contraindicates participation in the study

Criterion added with amendment 3:

E 25. Patients treated in advanced stage with any further chemotherapy/immunotherapy in addition to the therapies defined in I02

Exclusion criteria added with amendment 5 for eligibility for the crossover treatment phase (if implemented as detailed in Section 4.1.2)

A participant will be considered ineligible for the crossover treatment phase if any of the following criteria apply:

Medical conditions

E 801. Untreated brain metastases or history of leptomeningeal disease. Participants with newly diagnosed active brain metastases should be treated with local therapy (such as stereotactic radiosurgery), and treatment-related acute toxicities should be resolved before allocation to crossover tusamitamab ravtansine treatment.

E 802. Significant concomitant illnesses, including all severe medical conditions which, in the opinion of the investigator or Sponsor, would impair the patient's participation in the study or interpretation of the results.

E 803. Nonresolution of any prior treatment related toxicity to Grade <2 according to NCI CTCAE v5.0, except for alopecia, vitiligo, and active thyroiditis controlled with hormone replacement therapy.

E 804. Unresolved corneal disorders or any previous corneal disorder considered by an ophthalmologist to place the patient at higher risk of drug-induced keratopathy. The use of contact lenses is not permitted.

E 805. Medical conditions requiring concomitant administration of medications with a narrow therapeutic window that are metabolized by CYPs (See Appendix 9, Section 10.9) and for which a dose reduction cannot be considered.

E 806. 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 first administration of study intervention.

Prior/concomitant therapy

E 807. Participant received further line of anticancer treatment after docetaxel.

E 808. Concurrent treatment with any other anticancer therapy

E 809. Washout period before the first administration of tusamitamab ravtansine of less than 3 weeks from the last dose of docetaxel.

E 810. Any major surgery within the 3 weeks preceding the first crossover tusamitamab ravtansine treatment.

Prior/concurrent clinical study experience

E 811. Current participation in any other clinical study involving an investigational study treatment or any other type of medical research

Diagnostic assessment

E 812. The retreatment criteria as detailed in Section 6.6 are not met.

E 813. Poor renal function as eGFR <50 mL/min/1.73 m^2 per aMDRD formula

5.3 LIFESTYLE CONSIDERATIONS

Not applicable.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly 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 serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) and for whom resolution of the screen failure reason may not be expected within a reasonable time frame, the screen failure will be performed. In case the participant is a temporary screen failure (ie, prolonged screening), 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 temporary screen failure is a reason that might have altered the initial given agreement of the participant 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. If the participant screen failed, he/she may be rescreened; in this situation, the rescreened participant should sign a new study ICF (Section 10.1.3).

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.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, intended to be administered to a study participant according to the study protocol. Crossover tusamitamab ravtansine treatment will be handled in the same manner as treatment in the main study phase, as detailed below.

Infusion via a central line is preferred, if available. In case of participants with local intolerance after peripheral IV infusion, the decision to use a central line is left to the Investigator's decision.

Using an infusion-controlled pump, tusamitamab ravtansine will be administered by IV infusion over 1hour 30 minutes and docetaxel will be administered by IV infusion over 1 hour.

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.

On Day 1 of each treatment cycle, the patient's BSA will be determined using the current weight and baseline height; dose may not be adjusted if body weight change is ≤5%. For patients with a BSA >2.2 m^2, the dose will be calculated based on 2.2 m^2 BSA. After first study intervention of tusamitamab ravtansine, patients should be observed for acute reactions at site up to 4 hours depending on any sign of drug induced allergic reaction

Detail instructions for dilution and administration of the IMP is provided in Pharmacy Manual

Non-investigational medicinal product

Premedication

- *Premedication for tusamitamab ravtansine**:***

  Both SAR408701 and docetaxel had potential risk of infusion related allergic reaction and premedication should be used. All the drugs used as premedication will be entered to the concomitant premedication page.

  Premedication with histamine H1 antagonist (diphenylhydramine 50 mg PO or equivalent [eg, dexchlorpheniramine] given approximately 1 hour before tusamitamab ravtansine administration) is required for all participants. If a participant has previously experienced an infusion related 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 pre-medications can be discontinued at the discretion of the investigator.

- *Premedication for docetaxel:*

Premedication consisting of oral corticosteroid, such as dexamethasone 16 mg per day (eg, 8 mg BID dexamethasone or equivalent corticosteroids) for 3 days starting 1 day prior to docetaxel administration, unless contraindicated, can reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions. For docetaxel premedication, product leaflet or site guidance on administration of docetaxel will be followed.

6.1 STUDY INTERVENTION(S) ADMINISTERED

Table 2 - Overview of study interventions administered

ARM name	Tusamitamab ravtansine	Docetaxel
Intervention name	Tusamitamab ravtansine	Docetaxel
Type	Drug	Drug
Dose formulation	Concentrate for solution for intravenous infusion	Concentrate for solution for intravenous infusion
Unit dose strength(s)	5 mg/mL 125 mg/25mL	20 mg/mL 80 mg/4mL
Dosage level(s)	Tusamitamab ravtansine IV 100 mg/m² day 1 every 2 weeks	Docetaxel IV 75 mg/m² day 1 every 3 weeks
Route of administration	intravenous (IV) infusion	intravenous (IV) infusion
IMP and Ninvetigation	IMP	IMP
Packaging and labeling	Tusamitamab ravtansine (SAR408701) is supplied in a 30 mL type I glass vial with a white plastic flip-off cap. Each IMP kit contains 1 vial of 125 mg/25 mL of tusamitamab ravtansine, labeled with multilingual booklets. The content of the labeling at vial and box level is in accordance with the local regulatory specifications and requirements.	Docetaxel is supplied in a 7 mL clear colorless glass vial with a magenta plastic flip-off cap. Each IMP kit contains 1 vial of 80 mg/4 mL of Docetaxel, labelled with multilingual booklets. The content of the labeling at vial and box level is in accordance with the local regulatory specifications and requirements.
Current/Former name(s) or alias(es)	Tusamitamab ravtansine	TAXOTERE

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

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.

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.

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). Partially used and used study treatments will be destroyed at the study site according to the standard practices of the site after an accurate accountability has been performed and signed by the Investigator (or the pharmacist). A detailed treatment log form of the destroyed study treatment will be established with the Investigator (or the pharmacist) and countersigned by the Investigator and the Monitoring Team.

The Investigator must not destroy the unused IMP unless Sanofi provides written authorization.

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/ non-investigational medicinal product (NIMP) (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/NIMP 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/NIMP and eliminate potential hazards.

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

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

- The randomized intervention kit number list is generated centrally by Sanofi.
- The IMPs are packaged in accordance with this list.
- The IRT generates the participant randomization list and allocates the intervention number and the corresponding intervention kits to the participants according to it.
- During the trial, administration of tusamitamab ravtansine will be open-label, and no attempts will be made to blind administration. An IRT centralized randomization system will be used to prevent the investigators from knowing in advance the study intervention assignment, as the randomization is the best method to avoid bias.
- Despite the open-label administration of tusamitamab ravtansine, assessment of outcomes will be based on objectively collected data, which are radiological assessments for tumor response that will be reviewed by an IRC blinded to study intervention arms.
- Blinding rules for the Sponsor study team will be detailed in a separate document.

6.4 STUDY INTERVENTION COMPLIANCE

Administration of the IMP will be supervised by the Investigator or Sub-investigator. 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 person responsible for drug administration to the participant will precisely record the date and the time of the drug administration to the participant. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

6.5 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
- Route of use
- Dates of administration including start and end dates

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

- Docetaxel is a CYP3A4 substrate. *In vivo* studies showed that the exposure of docetaxel increased 2.2-fold when it was coadministered with ketoconazole, a potent inhibitor of CYP3A4. Protease inhibitors, particularly ritonavir, may increase the exposure of docetaxel. Concomitant use of docetaxel and drugs that inhibit CYP3A4 may increase exposure to docetaxel and should be avoided.
- Palliative radiotherapy may be given for control of pain for palliative intents. Sponsor should be notified to obtain prior approval prior to 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, hormone-replacement therapy, statin, antihypertensive medication) is allowed.
- Bone-targeting approved drugs (eg, bisphosphonate or denosumab) are allowed if there is no dose increase within 12 weeks prior to the randomization in the current study, and the patient remains at the same dosage throughout the study treatment.
- Supportive treatment as medically indicated for the patient's well-being may be prescribed at the Investigator's discretion. Every medication or treatment taken by the patient 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 anticancer 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 are allowed as detailed in Section 6.6.
- The use of prophylactic erythropoietin during the first cycle.
- Patients treated or intended to be treated with the following drugs presented as CYP substrates with narrow therapeutic range (NTR) should be carefully monitored (See Appendix 9 Table 17 [Section 10.9]).
- 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, Appendix 10 Table 18).
- The use of contact lenses will not be permitted during the study treatment period.

6.6 DOSE MODIFICATION

For the retreatment of patients on Day 1 of each subsequent cycle, the following conditions should be met:

- Neutrophils count $\geq 1.5 \times 10^9$/L.
- Platelets $\geq 100 \times 10^9$/L.
- Total bilirubin $\leq$1.5 x ULN.
- AST, ALT $\leq$2.5 x ULN or $\leq$5 x ULN in case of documented liver metastasis.
- No IMP-related toxicity Grade >1 (except for alopecia) or baseline severity.

Dose adjustment and/or cycle delay are permitted in case of adverse reaction. In case of toxicity, cycle delays and dose modifications should be implemented according to Appendix 4 (Section 10.4). Every effort will be made to administer the full dose regimen and maximize dose intensity.

Dose adjustments will be made according to 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 G-CSF should be administered according to the current American Society of Clinical Oncology (ASCO) guidelines (8). In case of neutropenia or febrile neutropenia, prophylactic G-CSF should be started and in case of second episode beside prophylactic G-CSF, then dose should be reduced.

The acceptable treatment windows for tusamitamab ravtansine and docetaxel administrations are 3 days and 4 days respectively.

One dose reduction is allowed for a participant in either arm in the main study or for a tusamitamab ravtansine crossover participant for a safety reason. Dose delay is allowed for safety management. Retreatment of patients that require more than 1 month dose delay need to be justified with case-by-case risk-benefit assessment. See Table 12 in Appendix 4 (Section 10.4) for guidance in dose modification or discontinuation. Approved product label should be followed for patient receiving docetaxel treatment for supportive care and dose modification requirement due to not listed adverse events. During the conduct of the study, if a second dose reduction may be needed, it should be decided upon case-by-case discussion with the Sponsor.

In case a dose reduction is necessary, the study intervention will be administered as follows:

Drug name	Starting dose	Reduced dose 1	Reduced dose 2[a]
Tusamitamab ravtansine	100 mg/m^2 Q2W	80 mg/m^2 Q2W	65 mg/m^2 Q2W
Docetaxel	75 mg/m^2 Q3W	60 mg/m^2 Q3W	50 mg/m^2 Q3W

a A second dose reduction for a participant for toxicity should be implemented only after discussion of the case with the Sponsor.

The same rules for study intervention dose modifications as well as safety management (Appendix 4 [Section 10.4]) are applicable for crossover tusamitamab ravtansine treatment.

6.7 INTERVENTION AFTER THE END OF THE STUDY

As per discretion of the Investigator.

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 documented progressive 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 assessment until PD and to be evaluated for survival status until OS cut-off date. See the SoA (Section 1.3) for data to be collected at the time of discontinuation of study intervention. Study intervention should be discontinued in any of the following cases:

1. Unacceptable AE.
2. Disease progression.
3. Poor compliance to the study protocol.
4. Other such as concurrent illness, that prevents further administration of study intervention.

For the patients who discontinue all study treatment after documented PD during or after main study treatment or crossover tusamitamab ravtansine treatment, survival status will be assessed every 12 weeks up to the OS study cut-off date.-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 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 assessment and immunogenicity sample, if appropriate.

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

7.1.2 Temporary discontinuation

Temporary intervention discontinuation (ie, prolonged cycle delay) 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 12 [Section 10.12]). For all temporary intervention discontinuations (ie, prolonged cycle delay), the duration should be recorded by the Investigator in the appropriate pages of the eCRF.

If the temporary discontinuation corresponds to more than 1 month delay of study intervention, all measures should be taken to ensure the participant's wellbeing, and the management plan for each ongoing patient should be guided by the clinical judgment of the treating physician based on an individual benefit-risk assessment and the evolving emergency situation.

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). The Investigator should discuss the restart of IMP after prolonged cycle delay with Sponsor's Medical Monitor.

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 intervention, if possible, an end of treatment visit should be conducted, as shown in the SoA (Section 1.3). 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 who withdrawn from the study 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 e-CRF 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. Participant decision to stop 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 rerandomized in the study or allocated to crossover tusamitamab ravtansine treatment. 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 (Section 1.3). Protocol waivers or exemptions are not allowed. For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 12, Section 10.12).
- 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.
- In patients who prescreened failed limited information will be collected as detailed in Section 1.3, to characterize patients that are most likely to express CEACAM5.

During screening period, demography, medical/surgical and disease history was evaluated. Demography includes age, gender, race, and ethnicity. Medical/surgical history includes relevant history of previous pathologies and surgeries. Disease history includes the histologic types, stage at diagnosis and disease extend at study entry, specific mutations including PD-L1 expression status and previous antitumor therapy (type, start and end dates, reason for discontinuation and response to the therapy) and smoking history.

Demographic data (age, gender, race, ethnicity, smoking status); age, histology and stage at diagnosis and biomarkers when available [tumor mutation status including PD-L1 expression status and circulating CEA) that collected during prescreening visit will be used for baseline demographic (except for age at prescreening) and disease characteristics analysis. Age, disease extend at study entry and previous antitumor therapy (type, start and end dates, reason for discontinuation and response to the therapy) and change in smoking history will be collected at screening visit. Age at screening will be considered as baseline demographic.

8.1 EFFICACY ASSESSMENTS

The assessment of PFS and OS with tusamitamab ravtansine compared to docetaxel are primary objectives.

All participants treated must have at least 1 measurable lesion as per RECIST 1.1for inclusion based on tumor assessment defined in SoA (see Section 1.3).

Tumor assessments will be made at every 8 weeks interval (±5 days window), and scheduled assessment time points will not be modified in case of a cycle delay. Thoracic-abdominal-pelvic CT-scan or MRI and any other examinations as clinically indicated will be performed to assess disease status at baseline, then every 8 weeks during the study treatment period until radiological disease progression or OS study cut-off, whichever comes first, and at the end of study treatment, except if already done at last cycle. Participants who have EOT visits due to other reasons than PD should continue tumor assessment until documented PD or OS study cut-off. Tumor assessment should be performed at EOT for patients and without imaging performed within past 4 weeks. Brain CT-scan or MRI should be performed at baseline and followed only for patients with brain lesions at baseline Imaging assessments are to be scheduled using the randomization date as the reference date for all time-points and are not to be scheduled based on the date of the previous imaging time-point. Imaging assessment delay to conform to treatment delay is not permitted. The same tumor assessment technique must be used throughout the study for a given lesion/participant.

The tumor assessment images, excluding those performed during crossover treatment phase, will be transferred to the Independent Radiological review Committee for tumor response evaluation.

Secondary efficacy variables will include the overall response rate (ORR) and the duration of response (DoR).

The RECIST 1.1 (Response Evaluation Criteria in Solid Tumors) criteria will be followed for assessment of tumor response, see Appendix 7 (Section 10.7) for details.

For participants who crossed over to tusamitamab ravtansine after progression on docetaxel treatment, tumor assessment will be performed per site local practice starting from first dose of crossover tusamitamab ravtansine treatment. There will be no central reading of tumor imaging, and efficacy assessments will be performed by the Investigator per RECIST 1.1. The Investigator will report the BOR and date of progression in the eCRF.

8.2 SAFETY ASSESSMENTS

Planned time points for all safety assessments are provided in the SoA (Section 1.3). Safety assessments for participants receiving crossover tusamitamab ravtansine treatment will be performed per SoA detailed in Section 1.3.2, and crossover safety analyses will be conducted separately from those for the main study phase.

8.2.1 Physical examinations

- A complete physical examination will include, at a minimum, assessments of the Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Height (at screening only) and weight will also be measured and recorded.
- ECOG performance status should be assessed before each IMP administration and at the follow-up visit.

- 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 Specific ocular test

Specific complete ocular tests at baseline and before the start of crossover tusamitamab ravtansine treatment will include the following: assessment of ocular/visual symptoms and ocular exams including visual acuity, slit lamp under dilatation, and Schirmer's test.

Standard specific ocular tests include:

- Assessment of ocular/visual symptoms, (ie, blurred vision, photophobia, dry eye) at each visit before each study intervention.
- Visual acuity at screening and whenever clinically indicated.
- Slit lamp under dilatation at screening and whenever clinically indicated.
- Schirmer's test at screening and whenever clinically indicated.
- 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 assessment by 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. Schirmer's test is mandatory for baseline assessment; it can be omitted from further ocular assessments if not considered a required examination per reported events category (ie, no symptom/findings of dry eye).

8.2.3 Vital signs

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

8.2.4 Electrocardiograms

- Single 12-lead ECG is required at baseline, at each cycle during first 4 cycles of tusamitamab ravtansine arm and 3 cycles for docetaxel arm and then every other cycle during treatment period (even cycles for tusamitamab ravtansine and odd cycles for docetaxel) and at end of treatment for both arms as outlined in the SoA (see Section 1.3).

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.

- In addition to before the infusion assessment, single 12-lead ECG is also required within 30 minutes after the EOI (End of Infusion) at Cycle 1 only for the tusamitamab ravtansine arm (see Section 1.3).
- Single 12-lead ECG will be obtained using an ECG machine that automatically calculates the heart rate and measures PR, QRS, and QT intervals.

8.2.5 Clinical safety laboratory assessments

- See Appendix 2 at Section 10.2 for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency.
- These tests will be done at each cycle. During first 2 treatment cycles of the main study phase as well as the crossover treatment phase, hematology, and liver function tests (ie, ALT, AST, ALP, and total and direct bilirubin) will be assessed weekly. If Grade 4 neutropenia occurs, assess ANC every 2-3 days until ANC $\geq 0.5 \times 10^9$/L. In case of Grade ≥3 liver function abnormal tests, additional tests will be done every 2 to 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.
- Troponin will be tested at baseline (at screening within 7 days of C1D1), at end of Cycle 4 for tusamitamab ravtansine and Cycle 3 for docetaxel, and at EOT visit. If the crossover treatment phase is implemented, troponin will be tested before the first dose of tusamitamab ravtansine at the Cycle 1-crossover visit; after the end of Cycle 4-crossover (before administration of tusamitamab ravtansine at the Cycle 5-crossover visit), and at the EOT-crossover visit.
- The Investigator must review the laboratory report, document this review.
- 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.

8.2.6 Guideline for management of adverse event

The docetaxel label should be followed for management of docetaxel specific adverse event if otherwise not specified in the protocol.

8.2.6.1 Hypersensitivity reactions

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

In case of event of hypersensitivity reactions, please refer to the recommended dose modification or discontinuation table (Table 12) in Appendix 4 (Section 10.4).

8.2.6.2 Ocular toxicity

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

The patient 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 on according to Study Procedures (Section 1.3). Ocular evaluation will be performed at baseline (during the screening period and as a baseline safety assessment before the start of the crossover treatment), as required during the treatment and at the EOT visit (ie, occurrence of ocular symptoms such as blurred vision, photophobia, pain), and when relevant, at FU visit(s). The outcome of the examination should be available before infusion of the next cycle. If ocular symptoms are present, then a formal ocular examination should be performed. In patients with any ocular/visual symptom(s) (eg, blurred vision, photophobia) the ocular evaluation should be repeated once weekly if not less frequent assessment recommended by ophthalmologist, until resolution to Grade 1. Then the patient should be followed with ocular exam (Slit Lamp and visual acuity) at each cycle until total resolution of the event.

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 discretion of ophthalmologist when applicable.

After resuming study treatment, the patient who had Grade ≥2 keratopathy/keratitis should be followed with standard ocular exams (ie, Slit Lamp examination under dilatation and Visual acuity) by every two cycles, even with no reported symptoms. If no recurrent event during the next four cycles, then regular follow-up (ie, symptom assessment at each visit with standard ocular exam in case of any ocular sign/symptom) is applied.

8.2.6.2.1 Keratopathy/keratitis management

Reversible non-inflammatory, microcystic keratopathy was identified as the DLT during the dose escalation process in 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 preferred term unless otherwise specified by ophthalmologist due to inflammatory findings on eye exams leading to 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 treatment period. Corticosteroid

containing ocular drugs are recommended in case ocular symptom occurs for the management of keratopathy/keratitis either and treatment will be performed based on discretion of ophthalmologist. Dose modification and recommendations are further described in Appendix 4 (Section 10.4).

8.2.6.3 Management of anemia

Patients should not start Cycle 1 treatment if hemoglobin is <9.0 g/dL. Red blood cell transfusion is allowed during the screening window, but a 2 weeks washout period should be applied. During the treatment, erythrocyte transfusion can be given, upon Investigator decision. Erythropoietin can be given based on the discretion of the Investigator, except during screening and first cycle. Current clinical guidelines should be followed for management of anemia.

8.2.6.4 Management of neutropenia

In patients who experienced either febrile neutropenia, neutrophil count <500 cells/mm^3 for more than 1 week during study intervention, the prophylactic G-CSF should be implemented to ensure dose intensity and the dose should be reduced in case of recurrent event even after prophylactic G-CSF use.

If the patient continues to experience these reactions at lower dose, the treatment should be discontinued (see Section 6.6).

8.2.6.5 Liver function tests

Hepatic enzyme increase has been reported with tusamitamab ravtansine and docetaxel administration as monotherapy. Patients should be carefully followed and in case of Grade ≥3 abnormal liver function tests, additional liver function tests will be done every 2-3 days until recovery to baseline value. Tusamitamab ravtansine should be permanently discontinued in case of drug induced Grade 4 liver enzyme increase. For stopping rules for docetaxel administration, current product leaflet should be followed.

Grade ≥3 increase events should be reported as adverse events of special interest (AESI).

8.2.6.6 Peripheral neuropathy

Patients with a known history of peripheral neuropathies and/or patients taking medications (eg, prior anti-tubulin, platinum, and/or taxanes treatments) known to cause peripheral neuropathies 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 10.4.

8.2.6.7 Gastrointestinal toxicity

Based on the clinical observation in TED13751 study, the following side effects have been observed regardless of causality: abdominal pain, colitis, constipation, diarrhea, dry mouth, erosive colitis (including ulcerative and hemorrhagic), nausea, stomatitis, and vomiting.

The monitoring of patients for GI toxicities will rely on careful evaluation by routine history and physical examination, and standard laboratory examination. Close surveillance of any signs and symptoms is required with additional routine blood hematology workup, Hemoglobin, hematocrit, WBC with differential, platelet counts, whenever indicated. As 1 case of Grade 4 erosive colitis reported, it is recommended to close surveillance of any diarrhea event with further exams when clinically indicated. Treatment is per patient condition based on investigator discretion.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 Adverse event of special interest

An adverse event of special interest (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 protocol amendment.

- Pregnancy of a female subject entered in a study as well as pregnancy occurring in a female partner of a male subject entered in a study with IMP/NIMP;
  - 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 Appendix 3, 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 Appendix 5, Section 10.5)
- Grade ≥3 keratopathy/keratitis
- Bundle branch blocks or any conduction defects
- Grade ≥3 liver enzyme increased (symptomatic or asymptomatic)
- Symptomatic overdose (serious or nonserious) with IMP/ NIMP
  - An overdose (accidental or intentional) with the IMP/NIMP is an event suspected by the Investigator or spontaneously notified by the participant and defined as at least 30% above the intended administered dose at each cycle expressed in unit per body surface.

The definitions of an AE or SAE can be found in Appendix 3 (Section 10.3).

AE 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 (Section 7).

8.3.2 Time period and frequency for collecting AE and SAE information

All SAEs will be collected from the signing of the screening ICF at the time points specified in the SoA (Section 1.3) and until at least D30 after the last study intervention administration.

All AE will be collected from the signing of the screening ICF at the time points specified in the SoA (Section 1.3) and until at least D30 after the last study intervention administration.

For participant who was prescreened and had fresh biopsy, only the Adverse Events related to the fresh biopsy procedure itself should also be reported in eCRF as general requirement of AE/SAE with the reporting time frame interval of 1 month for prescreening period after fresh biopsy).

For participants in Treatment Arm B crossing over to tusamitamb treatment during the Follow-up period, all AEs/SAEs/AESI will be reported starting from the date of the first dose of crossover tusamitamab ravtansine treatment up to 30 days after the last dose of tusamitamab ravtansine.

All SAEs and AESI 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 AE or SAE 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.

During follow-up period, SAEs regardless of relationship to IMP and IMP-related AEs, which are ongoing at the end of study treatment, and new IMP related AE/SAE, will be followed until resolution or stabilization.

8.3.3 Method of detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE 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.

8.3.4 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, and non-serious AEs of special interest (as defined in Section 8.3.1), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.2). Further information on follow-up procedures is given in Appendix 3 (Section 10.3).

8.3.5 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.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- Adverse events that are considered expected will be specified in the reference safety information.
- An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.6 Pregnancy

- Details of all pregnancies in [female participants and, if indicated, female partners of male participants] will be collected after the start of study intervention and until one year after the birth.
- If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 5 (Section 10.5).
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

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

The following disease related events (DREs) are common in participants with cancer and can be serious/life threatening:

- Progression of underlying disease, as it is the study endpoint.
- Death due to progression of underlying disease, if it occurs after 30 days of the last IMP administration. All death that occurs within the 30 days of last study intervention should be reported as a SAE.

Because these events are typically associated with the disease under study, they will not be reported according to the standard process for expedited reporting of SAEs even though the event may meet the definition of a SAE. These events will be recorded on the corresponding page in the participant's eCRF within the appropriate time frame. Lack of efficacy will not be reported as an AE/SAE, as it is part of efficacy analysis, but signs and symptoms due to lack of efficacy will be reported as AEs/SAEs as detailed in Section 10.3.

8.3.8 Guidelines for reporting product complaints

Any defect in the IMP/NIMP must be reported as soon as possible by the Investigator to the monitoring team that will complete a product complaint from 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. Guidance and information (contact and complaint form) are provided in the pharmacy manual and/or monitoring plan.

8.4 TREATMENT OF OVERDOSE

There is no specific antidote for treatment of overdose.

In the event of an overdose, the Investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.5 PHARMACOKINETICS

- For patients treated with tusamitamab ravtansine during the main study phase, samples of approximately 1 mL will be collected for measurement of plasma concentrations of tusamitamab ravtansine during Cycle 1 at predose (within 48 hours before Start of Infusion), end-of-infusion (EOI; ±10 min), and at D3 (ie, whenever between 24 hours and 72 hours after administration), at predose (within 24 hours before infusion) from Cycle 2 to Cycle 7, then every 6 cycles (ie, Cycles 13, 19, 25, etc…). At Cycle 3, in addition to the

predose sample, an EOI+1 hour (±10 minutes) sample will be collected. Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time of each sample will be recorded. These samples will be tested by the Sponsor's designee. Pharmacokinetic sampling times are summarized in Table 3.

Table 3 - Pharmacokinetic and antitherapeutic antibody sampling times and labeling

Cycle	Day within cycle	All participants treated with tusamitamab ravtansine in the main study phase[a]				
		Time point	Relative nominal time[b]	PK Sample ID	ATA sample ID	Time window allowance
Cycle 1 (first cycle of tusatumumab ravtansine)	1	SOI	0	P00	AB00	Within 24 hours before SOI
		EOI	1.5	P01	-	±10 minutes around the EOI
	3	48 hours	48	P04	-	Whenever between 24 and 72 hours
Cycle 2	1	SOI	0	P00	AB00	Within 24 hours before SOI. Sample must be collected even if tusamitamab ravtansine is not administered at this visit
Cycle 3	1	SOI	0	P00	AB00	Within 24 hours before SOI
		EOI+1 hour	2.5	P01	-	±10 minutes
Cycle 4	1	SOI	0	P00	-	Within 24 hours before SOI
Cycle 5	1	SOI	0	P00	-	Within 24 hours before SOI
Cycle 6	1	SOI	0	P00	-	Within 24 hours before SOI
Cycle 7	1	SOI	0	P00	AB00	Within 24 hours before SOI
Cycle 13 and every 6 cycles thereafter	1	SOI	0	P00	AB00	Within 24 hours before SOI

ATA=antitherapeutic antibody; EOI=end of infusion (ie, when the pump beeps before flush), PK=pharmacokinetic; SOI=start of infusion.

a Samples will be collected from all participants in the main study phase except the first 12 intensive PK participants treated in China

b Relative nominal times are calculated based on a theoretical infusion duration of 1 hour.

- Data from plasma concentrations of tusamitamab ravtansine will be used for population PK analysis by non-linear mixed effects modeling. Data from previously conducted studies might be added for model development. This analysis will involve an estimation of inter-patient PK variability, the determination of the population PK parameters estimates and the quantitative evaluation of potential effect of patient characteristics on the main PK parameters. Empirical Bayesian estimation of individual exposure parameters such as maximum concentration (C_{max}), trough concentration (C_{trough}) and area under the curve (AUC) will also be performed. Those individual exposure parameters will then be investigated as predictive factors for clinical outcomes including safety and efficacy endpoints, if possible.

The remaining plasma volume may also be used study for further exploratory analysis if deemed relevant.

8.6 PHARMACODYNAMICS

8.6.1 Circulating CEA

Circulating CEA levels collected at baseline and during the treatment and follow-up period at the time of laboratory assessment as close as to tumor assessment (and no more than 1-2 weeks) until disease progression 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.

Circulating CEA will be collected during the crossover tusamitamab ravtansine treatment every 4 cycles (ie, end of C4, C8, etc) at the time of routine safety lab assessment, before the next cycle.

8.7 GENETICS

A 20 mL blood sample corresponding to about 10 mL of plasma for tumor cfDNA isolation and an additional 2 mL blood sample for germline DNA will be collected at pre infusion of Cycle 1 Day 1 from participants to perform the required genetic tests (unless not allowed by local authorities). Samples are planned to be transferred to a centralized laboratory for cfDNA/DNA extraction and mutational profiling of key cancer genes to understand the significance of existing or acquired mutation during tusamitamab ravtansine treatment.

Fragmented 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.

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, TP53*.

8.8 BIOMARKERS

8.8.1 CEACAM5 expression in tumor tissue samples

At prescreening, determination of CEACAM5 positivity in tumors will be performed by IHC on FFPE slides collected from the most recent available tumor samples or if not available from a fresh biopsy. The tumor tissue samples could be from primary tumor biopsy or metastatic site, but bone lesions should be avoided, wherever possible. The level of CEACAM5 expression in tumor tissues at prescreening will be determined centrally using an in vitro diagnostic medical device provided by a third party. CEACAM5 IHC 769 assay is a qualitative immunohistochemical assay using monoclonal mouse anti-CEACAM5, Clone 769 intended for use in the detection of CEACAM5 protein in FFPE nonsquamous NSCLC tissue using EnVision FLEX visualization system on Dako Omnis platform. Analysis will be performed in a central laboratory and will be used to assess clinical validity of IHC assay to select patients with CEACAM5 high expression.

For the analysis, at least 5 × 4 µm slides from FFPE tissue block (ie, archive tumor tissue at diagnosis, archive tumor tissue at surgery, or most recent tumor sample) are required.

The positivity of CEACAM5 is defined by IHC with membrane staining at ≥2+ intensity of ≥50% of tumor cells.

8.9 IMMUNOGENICITY

For patients treated with tusamitamab ravtansine during the main study phase, blood samples of approximately 6 mL will be collected for measurement of antitherapeutic antibodies (ATAs) against tusamitamab ravtansine in plasma collected from all participants at predose Cycles 1, 2, 3, and 7, and then every 6 cycles (ie, at predose Cycles 13, 19, 25, …). It is required to collect the ATA samples at the same time of PK sampling of respective cycles. Additionally, blood samples should also be collected at the final visit from participants who discontinued study intervention or were withdrawn from the study (end-of-treatment (EOT). These samples will be tested by the Sponsor's designee or the sponsor himself.

Plasma samples will be screened for antibodies binding to tusamitamab ravtansine and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to tusamitamab ravtansine and/or further characterize the immunogenicity of tusamitamab ravtansine by evaluating for their ability to neutralize the activity of tusamitamab ravtansine. Table 3 summarizes sample collection times for immunogenicity assessments.

8.10 HEALTH ECONOMICS

Not applicable.

8.11 PATIENT-REPORTED OUTCOMES

Participants will complete electronic patient-reported outcomes (ePROs) at predose on Day 1 of Cycle 1 (up to within 3 days), then on Day 1 of every 2 docetaxel Cycles, or every 3 tusamitamab ravtansine Cycles (ie, every 6 weeks) at the end of treatment visit and one more time at first follow-up visit. Completed questionnaires (ePROs) are always considered source document and must be filed accordingly. Participants must complete ePROs in clinic (ePRO devices cannot be taken home) and prior to having any tests and to any discussion of their progress with healthcare personnel at the site. The instruments will be given to the participant in the appropriate language for the site. The time estimated to complete the EORTC QLQ-C30 and the EORTC QLQ LC13 is approximately 10 to 15 minutes.

There will be no ePRO assessment during the crossover tusamitamab ravtansine treatment phase.

8.11.1 EORTC QLQ-C30

The EORTC QLQ-C30 (C30) is a validated, self-administered, 30-item, cancer specific health related quality of life (HRQOL) questionnaire. (17). The C30 is a secondary endpoint in this study. The recall period for the C30 is the past week. The C30 assesses global health status/health-related quality of life (GHS/QoL), functioning, symptoms and financial difficulties due to disease or treatment related to cancer. For the GHS/QoL scale and the five functional scales (physical, role, emotional, cognitive, and social) higher scores indicate better GHS/QoL or function (higher scores better). C30 also assesses symptoms commonly reported by cancer patients and financial difficulties due to disease or treatment. For the three C30 symptom scales (fatigue, nausea & vomiting, and pain), five symptom items (dyspnea, insomnia, appetite loss, constipation, diarrhea and perceived financial difficulties item); lower scores indicate fewer symptoms/difficulties (lower scores better). Items on the C30 were scored using the C30 scoring algorithms which standardize the raw scores to a 0-100 range (18).

8.11.2 EORTC QLQ-LC13

The EORTC QLQ-LC13 (LC13) is the lung cancer module of the C30. The LC13 is a secondary endpoint in this study. The recall period for the LC13 is the past week. The LC13 assesses lung-cancer-associated symptoms (cough, dyspnea, pain, hemoptysis) and side-effects from conventional chemotherapy and radiotherapy (sore mouth, hair loss, dysphagia and neuropathy) that can impact the HRQOL of lung cancer patients (18). The EORTC QLQ-LC13 contains 13 items. Items on the LC13 were scored using the LC13 scoring algorithms which standardize the raw scores to a 0-100 range (18). Lower scores indicate lower symptomology/symptom burden (lower scores better).

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

This study is designed to test the following statistical set of hypotheses on PFS and on OS respectively as multiple primary endpoints:

H0: the survival distribution function of the tusamitamab ravtansine treatment group is lower or the same as the survival distribution function for the docetaxel treatment group

SDF (tusamitamab ravtansine) ≤SDF (docetaxel)

Versus

H1: the survival distribution function of tusamitamab ravtansine treatment group is superior to the survival distribution function of docetaxel treatment group

SDF(tusamitamab ravtansine) > SDF (docetaxel)

where SDF denotes the survival distribution function of the parameter PFS or OS respectively.

9.2 SAMPLE SIZE DETERMINATION

The sample size calculation incorporates multiplicity adjustment for the analyses of the multiple primary efficacy endpoints: progression free survival and overall survival.

Multiplicity of primary endpoints to calculate the sample size is taken into account using Bonferroni adjustment with different weights assigned to endpoints: PFS is tested at the 1-sided 0.01 level and OS is tested at the 1-sided 0.015 level for a strong control of the overall type-I error at the 2.5% level. The graphical method of Maurer and Bretz will be applied to provide a strong type-I error control for multiple hypotheses (Section 9.6).

Overall survival:

For OS, the following assumptions were used:

- OS has an exponential distribution in both treatment arms.
- The Docetaxel arm will have a median OS of 9 months.
- The tusamitamab ravtansine arm will have 28% risk reduction in hazard rate in comparison to Docetaxel arm. The targeted HR is 0.72, which corresponds to an improvement in the true median OS time from 9 months to 12.5 months.

- The first interim analysis for futility and efficacy assessment on OS is planned when approximately 221 PFS events or approximately 58% of OS events (approximately 210 deaths) are observed, whichever comes first.
- A second interim analysis of OS for assessment of efficacy is planned when 80% of the OS events (ie, approximately 290 deaths) are observed. Control of the type I error will be ensured using an O'Brien and Fleming spending function.
- A randomization ratio of 1:1.

With a total of 363 deaths, a log-rank test at an overall 1-sided 1.5% significance level will have 81% power to detect a risk reduction of 28% for tusamitamab ravtansine compared to docetaxel in OS.

Progression-free Survival:

For PFS, the following assumptions were used:

- Progression-free survival has an exponential distribution in both treatment arms.
- The docetaxel arm will have a median PFS of 4 months.
- The tusamitamab ravtansine arm will have 38.5% risk reduction in hazard rate in comparison to the docetaxel arm. The targeted HR is 0.615, which corresponds to an improvement in the true median PFS time from 4 months to 6.5 months.
- A randomization ratio of 1:1

With a total of 221 PFS events, a log-rank test at a 1-sided 1% significance level will have 90% power to detect a HR of 0.615 for tusamitamab ravtansine compared to docetaxel in PFS.

In case or reallocation of α following the multiplicity rules defined in Section 9.6,

- with 363 OS events at final OS analysis the study has ~86% power for detecting a HR of 0.72 at a 1-sided α of 0.0249 (see Table 9).
- with 221 PFS events at final PFS analysis the study has ~95% power for detecting a HR of 0.615 at a 1-sided α of 0.02485 (see Table 8).

Approximately 450 randomized participants (225 in each arm) would be adequate to achieve the targeted number of events for both PFS and OS.

Approximately 3534 participants will be prescreened for CEACAM5 status, of whom 530 patients will be screened to achieve 450 randomized patients with estimated failure rates of 85% for prescreening and 15% for screening.

Calculations assume the observed current enrollment at 3 participants per month during the first 7 months and assume 10 participants per month afterwards based on observed enrollment in the following year. Based on these enrollment assumptions, cut-off dates (CODs) for final analyses of PFS and OS would be approximately 40 and 58 months after FPI, respectively. These cut-offs

assume a dropout rate (censoring reason other than cut-off reached) of 17% at 4 months for the final analysis of PFS, and a probability of dropout of 3% at 58 months for the final analysis of OS.

Based on these assumptions, cut-off dates for 58% and 80% IAs of OS are planned approximately 40 months and 48 months after FPI, respectively.

Calculations were made using East 6.5.2 software.

9.3 POPULATIONS FOR ANALYSES

For purposes of analysis, the following populations are defined (Table 4):

Table 4 - 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.
Intent-to-treat (ITT)	All participants who have given their informed consent and who have had a treatment kit number allocated and recorded in the IRT. All analyses using this population will be based on the treatment assigned at randomization
Safety	All participants randomly assigned to study intervention and who have actually received at least 1 dose of study intervention. Participants will be analyzed according to the treatment arm they actually received.
Crossover - treated	All participants randomized to docetaxel arm and who have received at least 1 dose of tusamitamab ravtansine in the crossover phase. Analyses of safety and efficacy on the crossover phase will be performed in this population.
Pharmacokinetic	All participants from the safety population who have actually received at least 1 dose or a part of a dose of tusamitamab ravtansine in the main phase of the study with at least 1 evaluable concentration postbaseline with adequate documentation of dosing and sampling dates and times.
Immunogenicity	All participants from the safety population who have actually received at least 1 dose or a part of a dose of tusamitamab ravtansine in the main phase of the study with at least 1 evaluable postbaseline ATA result.

9.4 STATISTICAL ANALYSES

The statistical analysis plan will be developed and finalized before the FPI 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.

Planned date for analysis cut-off

The estimated COD is anticipated to be approximately 40 months after FPI for the final PFS/58% OS analyses. The CODs for the 80% OS interim analysis (at approximately 290 observed deaths) and final analysis of OS (at approximately 363 deaths observed) are anticipated to be approximately 8 and 18 months after the final PFS/58% OS COD, respectively (48 and 58 months after FPI).

9.4.1 Efficacy analyses

All efficacy analyses will be performed on the ITT population unless stated otherwise. All primary and secondary efficacy endpoints based on radiological assessments of tumor burden (ie, PFS, Objective Response Rate [ORR], and duration of response [DOR]) will be derived using the IRC tumor assessment. Analysis based on local radiologist's/Investigator's assessment will be considered as supportive analyses. A summary of efficacy analyses is provided in Table 5.

Table 5 - Efficacy analyses

Endpoint	Statistical Analysis Methods
Primary: PFS, OS	Stratified log-rank for statistical testing. Stratified Cox proportional hazard model for HR. Kaplan-Meier method for probabilities of being event free at different time points.
Secondary Key secondary ORR	Descriptive statistics by treatment arm and Clopper-Pearson method for CI calculation. Cochran-Mantel Haenszel for statistical testing.
Time to deterioration (EORTC QOL-C30 and LC13)	Stratified log-rank for statistical testing. Stratified Cox proportional hazard model for HR. Kaplan-Meier method for median time to deterioration
Other secondary DOR	Kaplan-Meier method for median duration of response
Exploratory Biomarkers (including CEACAM 5 expression at study entry)	Will be described in the SAP

CI = confidence interval; DOR = duration of response; HR = hazard ratio; OS = overall survival; ORR = objective response rate; PFS = progression-free survival; SAP = statistical analysis plan

9.4.1.1 Analysis of multiple primary efficacy endpoints

9.4.1.1.1 Progression Free Survival

Progression-free survival is defined as the time from the date of randomization to the date of the first documentation of objective PD according to RECIST 1.1 definitions or death due to any cause before the study cut-off date, whichever occurs first. Primary efficacy analysis will consist of PFS comparison between the tusamitamab ravtansine arm and Docetaxel arm through a log-rank test procedure stratified by the stratification factors as entered in the IRT. See Section 9.6 for details about the type-I error level to be used for statistical testing.

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

- If progression and death are not observed before the PFS analysis cut-off date, PFS will be censored at the date of the last valid disease assessment before the cut-off date with no evidence of a disease progression performed prior to the initiation of any posttreatment anticancer therapies.
- A participant without an event (death or disease progression) and without any valid postbaseline disease assessments will be censored at the day of randomization (Day 1).

The cut-off date for final analysis of PFS will be the date when approximately 221 PFS events or approximately 210 deaths are observed, whichever comes first.

The HR estimates and corresponding 95% and α-adjusted 2-sided CIs will be provided using the Cox proportional hazard model stratified by the same stratification factors as those used for the log-rank test described above. Progression-free survival for the 2 treatment arms will be summarized using Kaplan-Meier methods and displayed graphically. The median PFS times and associated 95% CI will be provided, along with probabilities of being progression-free at different time points.

Sensitivity analyses (eg, different censoring rules and PFS assessed by the Investigator) and subgroup analyses of PFS will be specified in the SAP.

9.4.1.1.2 Overall Survival

Overall survival is defined as the time from date of randomization to date of death due to any cause. If death is not observed before the OS analysis cut-off date, data on OS will be censored at the date the participant is known to be alive or at the OS cut-off date, whichever occurs first.

The cut-off date for the first IA will be the date when approximately 221 PFS events or approximately 210 deaths are observed, whichever comes first. Cut-off dates for the second interim and final analyses of OS will be when approximately 290 and approximately 363 deaths are observed, respectively.

Primary efficacy analysis will consist of OS comparison between the tusamitamab ravtansine arm and Docetaxel arm through a log-rank test procedure stratified by the stratification factors as entered in the IRT. See Section 9.6 for details about the type-I error level to be used for statistical testing.

The HR estimates and corresponding 95% and α-adjusted 2-sided CIs will be provided using the Cox proportional hazard model stratified by the same stratification factors as those used for the log-rank test described above. Overall survival for the 2 treatment arms will be summarized using Kaplan-Meier methods and displayed graphically. The median survival times and associated 95% CI will be provided, along with probabilities of being alive at different time points.

The significance levels at the interim and final analyses will be determined using O'Brien and Fleming α-spending function (see Section 9.5 and Section 9.6).

Sensitivity analyses and subgroup analyses of OS will be specified in the SAP. If the crossover tusamitamab ravtansine treatment phase is implemented, these may include especially analyses adjusting OS for switch to further systemic anticancer therapies (eg, using inverse probability of censoring weighting [IPCW] or Rank Preserving Structural Failure Time Model [RPSFTM] methods).

9.4.1.2 Analysis of secondary efficacy endpoints

Analysis of response-based endpoints (ie, ORR and DOR) and quality of life will be performed primarily on the ITT population.

9.4.1.2.1 Key secondary endpoints:

See Section 9.6 for details about the level of significance to be used for the CIs of the key secondary endpoints.

9.4.1.2.1.1 Objective response rate

The ORR on each randomized treatment arm will be estimated by dividing the number of participants with objective response (CR or PR as BOR, according to RECIST 1.1) by the number of participants from the analysis population of the respective treatment arm.

BOR is the best tumor response observed from the date of the randomization until disease progression, death, cut-off date, initiation of posttreatment anticancer therapy (including tusamitamab ravtansine initiated during the crossover), whichever occurs first.

ORR will be summarized for the ITT population with descriptive statistics at the time of the analysis of PFS. In addition, 2-sided CIs will be computed using the Clopper-Pearson method. Comparison between the tusamitamab ravtansine arm and the docetaxel arm will be performed using Cochran-Mantel Haenszel test with the stratification factors as entered in the IRT.
See Section 9.6 for details about the type-I error level to be used for statistical testing.

9.4.1.2.1.2 Time to deterioration in disease-related symptoms, time to deterioration in physical function, time to deterioration in role function

The time to deterioration (TTD) analyses will be conducted on the ITT population.

Health-related Quality of life (HRQL) is analyzed as TTD through 3 different secondary endpoints:

- TTD in disease related symptoms (composite endpoint of cough, chest pain and dyspnea) as determined by EORTC QLQ-LC13
- TTD in physical function (PF) as determined by EORTC QLQ-C30
- TTD in role function (RF) as determined by EORTC QLQ-C30

The TTD is defined as the time from baseline (Cycle 1, Day 1) until the first ≥10-point change from baseline (considered as clinically meaningful change) up to the end of treatment assessment before the initiation of further anticancer therapy and the analysis cut-off date.

For the TTD in disease-related symptoms (cough, dyspnea, pain) from EORTC QLQ LC-13, a deterioration will be defined as an increase from baseline score of at least 10 points in any 1 of these 3 symptoms. For TTD in PF and RF from EORTC QLQ-C30, a deterioration will be defined as a decrease of at least 10 points from baseline score.

Participants with a non-missing baseline assessment will be censored at the last assessment up to end of treatment before the start of further anticancer therapy or before the analysis cut-off date (whichever is earlier), provided their symptoms/functional scale had not deteriorated up to that point before the analysis cut-off date. A participant without a baseline or postbaseline PRO questionnaire or whose baseline scores do not allow further deterioration will be censored at the first administration intake (or at randomization date if the participant is randomized and not treated).

Efficacy analysis will consist of time to deterioration comparison between the tusamitamab ravtansine arm and docetaxel arm through a log-rank test procedure stratified by the stratification factors as entered in the IRT. See Section 9.6 for details about the type-I error level to be used for statistical testing.

The HR estimates and corresponding 2-sided CIs will be provided using the Cox proportional hazard model stratified by the same stratification factors as those used for the log-rank test described above. Time to deterioration for the 2 treatment arms will be summarized using Kaplan-Meier methods and displayed graphically. The median time to deterioration and associated 95% CI will be provided.

Sensitivity analyses and supportive analyses of the 3 TTD endpoints will be specified in the SAP.

9.4.1.2.2 Other secondary endpoints:

9.4.1.2.2.1 Duration of response

The DOR will only be summarized on the subgroup of participants who have achieved objective response in the ITT population.

The duration of response (DOR) will be defined as the time from the date of first initial occurrence of a CR or PR to the date of first documentation of objective PD according to RECIST 1.1 before the initiation of any posttreatment anticancer therapy or death due to any cause, whichever occurs first.

For participants with ongoing response at the time of the analysis, DOR will be censored at the date of the last valid disease assessment not showing disease progression performed before the initiation of any posttreatment anticancer treatment or the analysis COD, whichever occurs first. Duration of response for the 2 treatment arms will be summarized using Kaplan-Meier methods and displayed graphically, if appropriate. The median DOR and associated 95% CI will be provided.

9.4.1.3 Analysis of exploratory efficacy endpoints

The ORR based on local radiologist's/Investigator's assessment on the crossover period will be summarized in the crossover treated population. For crossover participants, BOR will be reported by the Investigator.

9.4.2 Safety analyses

All safety analyses will be primarily performed on the Safety Population by actual treatment group. For participants who enter the crossover phase to receive tusamitamab ravtansine treatment, analyses on the safety population will include all data reported up to the crossover date. Safety analyses will be performed separately on the crossover treated population. Summary of safety data will be performed by participant. For each of the safety parameters, a baseline value will be defined as the last value or measurement taken up to the first dose in the study. For a participant who crosses over to tusamitamab ravtansine, a crossover baseline value will be defined as the last value or measurement taken up to the first dose of tusamitamab ravtansine in the crossover phase.

A summary of safety analyses is provided in Table 6.

Table 6 - Safety analyses

Endpoint	Statistical Analysis Methods
Primary	No primary endpoint is defined for safety analyses.
Secondary AEs/SAEs and laboratory abnormalities	Descriptive statistics
Exploratory Immunogenicity	Will be described in the SAP

AE = adverse event; SAE = serious adverse event; SAP = statistical analysis plan.

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 dose of IMP up to 30 days after the last dose of IMP. For participants randomized to docetaxel who enter the crossover phase to receive tusamitamab ravtansine treatment, the treatment period is defined as the time from the first dose of IMP up to the last dose of IMP before the crossover +30 days, or up to the first dose of tusamitamab ravtansine –1 day, whichever is earlier.
- The crossover treatment period is defined as the time from the first dose of tusamitamab ravtansine after crossover up to 30 days after the last dose of tusamitamab ravtansine.

- The posttreatment period is defined as the time starting 31 days after the last dose of IMP (including the crossover treatment phase) to study closure or death, whichever comes first.

9.4.2.1 Analyses of adverse events

Adverse events will be graded according to NCI-CTCAE v5.0 and classified by system organ class (SOC) / preferred term (PT) according to the last available version of the MedDRA dictionary.

- Prescreening AEs are defined as AE occurring during the prescreening period.
- Screening AEs are defined as any AE 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.
- Crossover treatment-emergent AEs are defined as AEs that develop, worsen (in the opinion of the Investigator), or become serious during the crossover treatment phase.
- Posttreatment AEs are defined as AEs that are reported during the posttreatment period.

The grade will be taken into account in the summary. 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 posttreatment AEs will be described separately.

9.4.2.1.1 Treatment-emergent adverse events

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

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

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 safety 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 posttreatment period.

In addition, an overview of Grade 5 AEs will be provided summarizing the number (%) of participants with any:

- Grade 5 AE (TEAE and posttreatment)
- Fatal TEAE
- Grade 5 TEAE (TEAE with a fatal outcome during the treatment period)
- Any grade TEAE with a fatal outcome during the posttreatment period.
- Posttreatment Grade 5 AE (excluding a TEAE that worsened to Grade 5 during the posttreatment period)

Selected summaries of crossover TEAEs will be provided for the crossover treated population.

9.4.2.2 Deaths

The following summaries of deaths will be generated:

- Number (%) of participants who died by study period (treatment, crossover treatment [if applicable], posttreatment) and reasons for death (disease progression, AE, or other reason).
- Deaths in non-randomized participants or randomized but not treated participants.
- All TEAEs leading to death by primary SOC and PT showing number (%) of participants.

Similar outputs will be provided for the crossover treated population.

9.4.2.3 Analyses of 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 blood chemistry results will be graded according to the NCI-CTCAE v5.0, when applicable. Number and percentage of participants with laboratory abnormalities (ie, all grades and by grade) using the worst grade during the treatment period (or crossover treatment period, as applicable) will be provided for the safety population (and crossover treated population, as applicable).

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

9.4.2.3.1 Analysis of immunogenicity

Incidence of ATAs will be provided for the immunogenicity-evaluable population. Immunogenicity analysis and the potential impact on PK, safety and efficacy will be described in the SAP.

9.4.3 Other analyses

The population PK analyses will be described in the Population PK analysis plan (PAP) provided by PKDM Modeling and Simulation group. The results of the population PK analysis will be presented separately from the main clinical study report (CSR).

Biomarker analyses (including CEACAM5 at study entry) and exploratory PK relationship with efficacy, safety and other biomarker will be described in the SAP.

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.

9.5 INTERIM ANALYSES

The Statistical Analysis Plan will describe the planned IAs in greater detail.

A first IA for efficacy and futility assessment on OS will be performed when approximately 221 PFS events or approximately 210 deaths (58% of OS events) are observed, whichever comes first. At that time, final PFS analysis will also be performed. The cut-off date for final analysis of PFS and 58% IA of OS will be approximately 40 months after FPI. A second IA for efficacy assessment of OS will be performed when approximately 80% of targeted number of deaths will be available (ie, approximately 290 deaths). The cut-off date for the second IA of OS will be approximately 48 months after FPI.

The futility rule of the first IA is described below. Of note, the stopping boundaries for the nonbinding futility assessment will be based on the observed OS HR using a Cox proportional-hazard model stratified by the stratification factors as entered in the IRT. If the observed OS HR is >0.90, then the study may be stopped (nonbinding futility assessment). Table 7 summarizes the probabilities of crossing the futility boundary under different assumptions for the true HR. In addition, the predictive power for the final analysis of OS given the interim data could be used as supportive information to guide the decision.

Table 7 - Probabilities of crossing the futility boundary on overall survival under different assumptions for the true hazard ratio

H_0 (HR=1)	HR=0.95	HR=0.85	HR=0.80	H_1 (HR=0.72)
77.7%	65.2%	33.9%	19.7%	5.3%

Abbreviations: H_0=null hypothesis (nonsuperiority of tusamitamab ravtansine treatment to docetaxel treatment); H_1: superiority of tusamitamab ravtansine treatment to docetaxel treatment; HR=hazard ratio.

The stopping boundaries for efficacy on the OS endpoint will be derived based on the O'Brien and Fleming α-spending function for type I error and will depend on the actual number of events observed at the time of each interim analysis.

If exactly 210 deaths are observed (58% information fraction), and exactly 290 deaths (80% information fraction) are observed respectively at the time of the first and second IAs of OS, boundary properties for the planned IAs of overwhelming efficacy for OS are detailed in Table 9.

The 1-sided nominal significance level to declare superiority of tusamitamab ravtansine at the final analysis (approximately 363 deaths) is 0.0130 (the corresponding threshold for the observed HR to reach this significance level is 0.792).

The analysis on PFS will not be updated at the time of any subsequent OS analysis. If this primary analysis on PFS is significant, this analysis will be used to support registration of tusamitamab ravtansine. Regardless of the PFS data, the study will continue until the final analysis of OS, unless either interim analysis of OS shows overwhelming efficacy or futility. Note that if futility is shown, the Sponsor may still decide to continue the study (nonbinding properties).

At the time of the 58% interim analysis of OS, the conditional power for final analysis of OS based on the observed OS data until that time point will be examined, considering the potential impact on the power for the final OS analysis, to assess whether the tusamitamab ravtansine crossover phase can be implemented.

9.5.1 Data Monitoring Committee (DMC)

This study will use an independent DMC. Details on DMC structure and role are presented in Section 10.1.5.

The first DMC meeting will be set up to review early safety results (eg, after approximately 50 participants enrolled into the study or after 6 months after first participant randomized whichever comes earlier), and then periodically. Ad hoc DMC meetings may also be held if a significant safety issue or an issue deemed important for discussion arises on this or other tusamitamab ravtansine studies. After each meeting, the DMC will make recommendations to the Sponsor's representatives regarding the continued safety of treating ongoing and future study participants, as well as the course of action regarding the conduct of the study.

During the course of the study, an external statistician (independent from the sponsor) will perform the unblinded final analysis of PFS and interim analyses of OS, as well as unblinded interim safety and efficacy analyses for the purpose of the DMC data review. Access to these data and analyses will be restricted to the DMC members and to limited personnel from the Sponsor involved in the submission, if applicable.

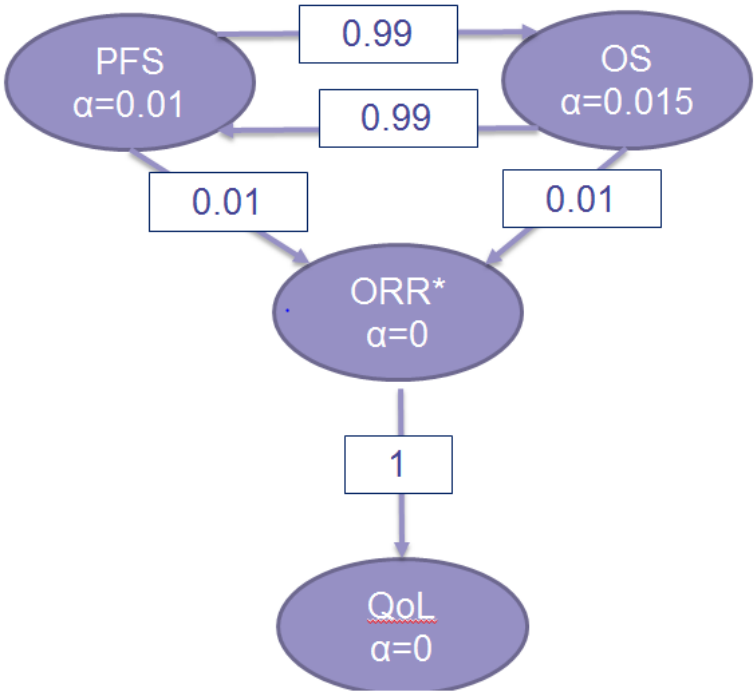
For the final analysis of PFS and the IAs of OS, after review of the results by arm, the DMC will make recommendations on continuation of the study or not, and on unblinding or not according to the criteria prespecified by the Sponsor.

9.6 MULTIPLICITY

The trial uses the graphical method of Maurer and Bretz (19) to provide a strong type-I error control for multiple hypotheses. Figure 1 shows the initial 1-sided α-allocation for each

hypothesis (in the ellipse) on the endpoints of PFS, OS, ORR and QoL. The weights for reallocation from each hypothesis to the others are represented in the boxes on the lines connecting hypotheses.

Figure 2 - Type I error reallocation strategy



*If both PFS and OS are significant, based on the graphical testing procedure, the entire α=0.025 will be reallocated to the testing of ORR.
Abbreviations: ORR=objective response rate (complete response +partial response) OS=overall survival; PFS=progression-free survival; QoL=quality of life.

PFS

PFS hypothesis will be tested at α=0.01. When OS test is significant, the PFS hypothesis may be tested at α=0.02485 (0.99*0.015+0.01) (re-allocated α).

Table 8 demonstrates the bounds and boundary properties for PFS hypothesis testing. The HR of PFS between the experimental group and control group is assumed to be 0.615.

Table 8 - Boundary properties for planned final analysis of PFS

	Boundary	α=0.01	α=0.02485
IF: 100%			
N: 351	Critical value	-2.326	-1.963
Events: 221	Threshold for the observed HR to be significant	0.731	0.768
Months:40	Prob of significant if true HR=0.615	0.901	0.951

With 221 PFS events at final analysis the study has ~95% power for detecting a HR of 0.615 at a 1-sided α of 0.02485.

OS

The OS hypothesis will be tested at α=0.015. When PFS test is significant, the OS hypothesis may be tested at α=0.0249 (0.99*0.01+0.015) (re-allocated α). Table 9 demonstrates the bounds and boundary properties for OS hypothesis testing. The HR of OS between the experimental group and control group is assumed to be 0.72. The table summarizes the α spending for interim and final analyses based on the planned number of events. The actual α spending will be based on the actual number of events included in the analyses and determined by the Lan-DeMets O'Brien-Fleming spending function at the time of interim and final analyses.

Table 9 - Boundary properties for planned analyses of OS

Analysis	Boundary	α=0.015	α=0.0249
First IA			
IF: 58%	Critical value	-2.992	-2.728
N: 351	Significance level (1-sided)	0.0014	0.0032
Events: 210	Threshold for the observed HR to be significant	0.662	0.686
Months: 40	Prob significant if true HR=1	0.0014	0.0032
	Prob significant if true HR=0.72	0.2702	0.3641
Second IA			
IF: 80%	Critical value	-2.508	-2.287
N: 436	Significance level (1-sided)	0.0061	0.0111
Events: 290	Threshold for the observed HR to be significant	0.745	0.764
Months: 48	Cumulative prob significant if true HR=1	0.0065	0.0120
	Cumulative prob significant if true HR=0.72	0.6178	0.6997
Final			
IF: 100%	Critical value	-2.227	-2.031
N: 450	Significance level (1-sided)	0.0130	0.0211
Events: 363	Threshold for the observed HR to be significant	0.792	0.808
Month: 58	Cumulative prob of significant if true HR=1	0.0145	0.0236
	Cumulative prob of significant if true HR=0.72	0.8143	0.8573

Abbreviations: IA=interim analysis; IF=information fraction; HR=hazard ratio; prob=probability.

ORR

Following the graphical testing procedure, the ORR hypothesis will be tested at the following α level shown in Table 10 depending on the results from testing PFS and OS**.** ORR will be tested if either PFS or OS is significant.

Table 10 - ORR hypothesis testing level

α level for testing ORR hypothesis	Condition
0.0001	if only PFS is significant, and OS is not significant
0.00015	if only OS is significant at either IA or final analysis, and PFS is not significant
0.025	if PFS is significant and OS is significant at either IA or final analysis

Abbreviations: IA=interim analysis; OS=overall survival; PFS=progression-free survival.

Then, a user-defined spending function will be applied to the α level using a fixed α level of 0.00001 for ORR hypothesis testing at each IA, and a fixed α level for final analysis, computed as (α level for testing ORR [as defined in Table 10] - 2 × 0.00001).

TTD endpoints for QoL

If ORR is significant, then QoL key secondary endpoints will be tested at the same significance level as ORR following a hierarchical order: TTD in disease-related symptoms, TTD in physical function, TTD in role function. The procedure, including the user-defined α-spending function, is similar to the hypothesis testing of ORR.

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 Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, 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.
- 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
  - 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), and all other applicable local regulations

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 participant and answer all questions regarding 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, 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.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

A participant who requires prolongation of the screening period (temporary screen failure) is not required to sign another ICF. Participants who screen failed and then rescreen need to re-sign a new screening ICF; there will be no re-prescreening for CEACAM5 expression and initial value will be applicable, with respect to maximum allowed window for prescreening.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The Investigator or authorized designee will explain to each participant the objectives of the exploratory 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. A separate signature will be required to document a participant's agreement to allow any remaining specimens analysis to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate signature.

10.1.4 Data protection

All personal data collected related to participants, Investigators, or any person involved in the study, which may be included in the Sponsor's databases, shall be treated in compliance with all applicable laws and regulations including the GDPR (Global Data Protection Regulation).

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 these data are required by several regulatory agencies (eg, on afro American population for the FDA or on Japanese population for the Pharmaceuticals and Medical Devices Agency in Japan).

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant

names or any information which would make the participant identifiable will not be transferred.

- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- 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.
- When archiving or processing personal data pertaining to the Investigator and/or to the participants, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

10.1.5 Committees structure

Data Monitoring Committee (DMC):

Independent from the Sponsor and Investigators, the DMC role will include 3 external members (2 oncologists and 1 statistician) and will meet regularly to:

- Review progress of the trial
- Review the safety of data
- Advise the sponsor and the study chairmen on potential modifications or communications that may be necessary to ensure the participant safety or protect the scientific integrity of the trial.

The DMC will also be in charge of reviewing the formal interim analysis for OS and the final analyses for PFS (please see Section 9.5.1).

Specific details regarding composition, roles and responsibilities, governance, requirements, and documentation of DMC reports will be described in the DMC charter.

DMC may invite ad hoc experts (eg, ophthalmologist) for safety follow-up, when relevant.

Independent Radiological review committee (IRC):

Independent from the Sponsor and Investigators, the IRC will review the tumor assessment data as central reading for response evaluation in blinded manner.

All the tumor assessment imaging performed during the main study phase will be sent for central review. The same modality of tumor assessment should be used throughout the study for each individual patient. Treatment continuation will be decided by investigator according to response evaluation by local radiologist/ Investigator but statistical analyses for efficacy parameters of the main study phase will be performed based on IRC.

Process will be defined in related manuals.

10.1.6 Dissemination of clinical study data

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, clinicaltrialsregister.eu, 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.

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.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- 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).
- 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.

- 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

- 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.
- 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.

10.1.9 Study and site closure

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 the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- 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 recruitment of participants by the Investigator
- Discontinuation of further study intervention development

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 multicenter 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 11 will be performed by the local 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 will be performed in all WOCBP at baseline and at end of treatment visit, as detailed in 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 end of treatment evaluation (between D22 and D30 after the last IMP administration). The serum/urine pregnancy test will also be performed before each cycle, only in countries where it is a regulatory requirement.

Table 11 - Protocol-required safety laboratory assessments (local laboratory)

Laboratory assessments	Parameters
Hematology	
	Platelet count Hemoglobin Hematocrit White blood cell (WBC) count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Coagulation	INR
Blood chemistry[a]	Urea or Blood urea nitrogen (BUN) Creatinine Glucose LDH Albumin Potassium Sodium Calcium Phosphate Chloride Magnesium Bicarbonate[b] Aspartate aminotransferase (AST)/ Serum glutamic-oxaloacetic transaminase (SGOT) Alanine aminotransferase (ALT)/ Serum glutamic-pyruvic transaminase (SGPT) Alkaline phosphatase Total bilirubin and conjugated bilirubin Total protein Troponin
Other screening tests	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • 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] ± Hepatitis B core Antigen or Hepatitis B Viral DNA, and hepatitis C virus antibody or other tests) if applicable as per local regulatory requirement] The results of each test must be entered into the CRF

NOTES:

a Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 8.2.6.5. All events of grade ≥3 AST/ALT increase should be reported as adverse events of special interest (AESI).

b Bicarbonate may be omitted at countries where its assay is not performed as part of the routine chemistry panel.

c Serum pregnancy test will be performed at screening and end of treatment. If required to repeat during treatment period, 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: ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

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.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, blood 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 fulfil the definition of 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.

DEFINITION OF SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:

a) Results in death

b) 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.

c) Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (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.

d) Results in persistent 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.

e) Is a congenital anomaly/birth defect

f) Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be

immediately life-threatening or result in death or hospitalization but 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.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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 in the CRF.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to Monitoring team in lieu of completion of the Sanofi/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Sanofi. 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 Monitoring team.
- 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 NCI CTCAE v5.0:

An event is defined as "serious" when it meets at least 1 of the predefined 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 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 Investigator's Brochure (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 Sanofi. 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** Monitoring Team**.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send a 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 Monitoring Team 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.
- New or updated information will be recorded in the originally completed CRF.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

REPORTING OF SAES

SAE reporting to Sanofi **via an electronic data collection tool**

- The primary mechanism for reporting an SAE to Monitoring Team 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) in order 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 Monitoring Team by telephone.

- Contacts for SAE reporting can be found in Investigator Study File.

SAE reporting to Sanofi via paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the Monitoring Team.
- 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 Investigator Study file.

10.4 APPENDIX 4: RECOMMENDED SUPPORTIVE CARE AND/OR DOSE MODIFICATION GUIDELINES FOR DRUG-RELATED ADVERSE EVENTS

Table 12 - Recommended dose modification or discontinuation

Event	Symptoms severity (Nadir) (NCI CTCAE v5.0)	Management of IMP dosing (tusamitamab ravtansine)	Management of IMP dosing (Docetaxel) (20;21)	Supportive care guidelines
Infusion related reaction	Mild-moderate Eg, Grade ≤2 nausea, headache, tachycardia, hypotension, rash, shortness of breath.	Interrupt tusamitamab ravtansine infusion. SAR408701 may be resumed only after patient recovery, at half the previous infusion rate.[a]	Interrupt Docetaxel infusion and start appropriate treatment.	Give diphenhydramine 50 mg IV and/or dexamethasone 10 mg IV. Docetaxel label should be followed Dexamethasone can be added as premedication for upcoming cycles for SAR408701
	Severe Eg, symptomatic bronchospasm, urticaria lesions covering >30% BSA, hypotension, angioedema.	Interrupt tusamitamab ravtansine infusion and definitively discontinue tusamitamab ravtansine.	Interrupt docetaxel infusion and definitively discontinue docetaxel	Give diphenhydramine 50 mg IV and/or dexamethasone 10 mg IV and/or epinephrine and any required treatment per investigator judgement.

Event	Symptoms severity (Nadir) (NCI CTCAE v5.0)	Management of IMP dosing (tusamitamab ravtansine)	Management of IMP dosing (Docetaxel) (20;21)	Supportive care guidelines
Ocular toxicity: Keratopathy/keratitis[b] associated with tusamitamab ravtansine (Cystoid macular edema associated with docetaxel)	Grade 1 – Asymptomatic; clinical or diagnostic observations only; intervention not indicated .	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).	Cystoid macular edema has been reported with docetaxel. Patients with impaired vision should undergo a prompt and complete ophthalmologic examination. In case CMO is diagnosed, docetaxel treatment should be discontinued and appropriate treatment initiated (21)	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.		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 2 cycles, even asymptomatic during next 4 cycles. If no recurrence, standard process with follow-up with ocular symptom is resumed, as detailed in Section 8.2.6.2.
	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.		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 4 Perforation, best corrected visual acuity of 20/200 or worse in the affected eye	Definitive discontinuation of tusamitamab ravtansine.		Complete the corneal examination as recommended by ophthalmologist. Repeat the standard ocular examination weekly[c] until resolution[d]. Start curative treatment per ophthalmologist recommendation.

Event	Symptoms severity (Nadir) (NCI CTCAE v5.0)	Management of IMP dosing (tusamitamab ravtansine)	Management of IMP dosing (Docetaxel) (20;21)	Supportive care guidelines
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.	Not expected	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.		ECG to be repeated twice weekly until event resolution. Prompt cardiology consultation Additional evaluations such LVEF and Holter monitoring should be performed when relevant.
Neutrophil count decreased	Grade 1 <LLN – 1500/mm^3; <LLN – 1.5 × 10^9/L	No change in IMPs administration.	No change in IMPs administration	No intervention.
	Grade 2 <1500 – 1000/mm^3; <1.5 – 1.0 × 10^9/L	Delay the cycle until recovery of absolute neutrophil count >1500/mm^3. Restart at the same dose.	Delay the cycle until recovery of absolute neutrophil count >1500/mm^3. Restart at the same dose.	No intervention.
	Grade 3 <1000 – 500/mm^3; <1.0 – 0.5 × 10^9/L Or Grade 4 <500/mm^3; <0.5 × 10^9/L	Delay the cycle. Restart the treatment when absolute neutrophil count >1500/mm^3 at the same dose. Prophylactic G-CSF can be considered in all subsequent cycle	Delay the cycle. Restart the treatment when absolute neutrophil count >1500/mm^3 at the same dose and add G-CSF to provide prophylactic coverage in all subsequent cycles. If reoccurred under the prophylactic G-CSF treatment, dose reduction might be considered case by case manner (eg, Asian patient with higher risk of hematologic toxicity)	Follow ASCO guidelines on usage G-CSF and antibiotherapy (22). Repeat the test every 3 days.

Event	Symptoms severity (Nadir) (NCI CTCAE v5.0)	Management of IMP dosing (tusamitamab ravtansine)	Management of IMP dosing (Docetaxel) (20;21)	Supportive care guidelines
	Grade 4 >7days <500/mm^3; <0.5 × 10^9/L	Delay the cycle until absolute neutrophil count >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	Delay the cycle until absolute neutrophil count >1500/mm^3. 1st episode administer next cycle at the same dose and prophylactic G-CSF should be implemented 2nd episode: administer docetaxel at reduced dose 3rd episode: definitive discontinuation	Follow ASCO guidelines on usage G-CSF and antibiotherapy (22). Repeat the test every 3 days.
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 absolute neutrophil count >1500/mm^3. 1st episode administer next cycle at the same dose and administer G-CSF 2nd episode: administer tusamitamab ravtansine at reduce dose 3rd episode: definitive discontinuation	Delay cycle until absolute neutrophil count >1500/mm^3. 1st episode administer next cycle at the same dose and administer G-CSF 2nd episode: administer docetaxel at reduce dose 3rd episode: definitive discontinuation	To ensure relative dose ıntensity, G-CSF is recommended as secondary prophylaxis in all patients with Grade ≥3 febrile neutropenia ASCO guideline is recommended for supportive treatment if there are no defined clinical standards (22).
	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	Administration changes to be decided at the Investigator's discretion: 1st episode: administer next cycle at reduce dose and administer G-CSF or definitively discontinue 2nd episode: definitive discontinuation	

Event	Symptoms severity (Nadir) (NCI CTCAE v5.0)	Management of IMP dosing (tusamitamab ravtansine)	Management of IMP dosing (Docetaxel) (20;21)	Supportive care guidelines
Peripheral neuropathy	Grade 1: Asymptomatic	No action	No action	Patient 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	Delay cycle, dose reduction if no improvement with dose delay	
	Grade 3: Severe symptoms; limiting self care Activities of Daily Living	Definitive discontinuation	Definitive discontinuation	
	Grade 4: Life-threatening consequences; urgent intervention indicated	Definitive discontinuation	Definitive discontinuation	

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.

Abbreviations: 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.

10.5 APPENDIX 5: CONTRACEPTIVE GUIDANCE AND COLLECTION OF PREGNANCY INFORMATION

DEFINITIONS:

Woman of childbearing potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

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

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - 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), Investigator discretion should be applied to determining study entry.

   Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 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 hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
   - 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.

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[b]
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)[b]
- Bilateral tubal occlusion
- Vasectomized partner

(Vasectomized partner 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. Spermatogenesis cycle is approximately 90 days.)

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.)

ACCEPTABLE METHODS[d]

- Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action
- Male or female condom with or without spermicide[e]
- Cervical cap, diaphragm, or sponge with spermicide
- A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]

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.

d Considered effective, but not highly effective - failure rate of ≥1% per year. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception.

e Male condom and female condom should not be used together (due to risk of failure with friction).

COLLECTION OF PREGNANCY INFORMATION:

Male participants with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date but may last up to one year. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female participants who become pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date but may last up to one year. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- Any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. 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 8.3.5. While the Investigator is not obligated to actively seek this information in former study participants, 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.

10.6 APPENDIX 6: GENETICS

Use/Analysis of DNA

- 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 analysis from consenting participants.
- DNA samples will be used for research related to tusamitamab ravtansine or nonsquamous NSCLC and related diseases. They may also be used to develop tests/assays including diagnostic tests related to CEACAM5 targeting drugs and nonsquamous NSCLC. 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 samples will be analyzed for determination of tumor mutation profile on plasma cfDNA. 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 samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on tusamitamab ravtansine, CEACAM5 target or lung cancer continues but no longer than 15 years or other period as per local requirements.

10.7 APPENDIX 7: RESPONSE EVALUATION CRITERIA IN SOLID TUMORS VERSION 1.1

Details provided in bibliographic reference (23).

Measurability of tumor at baseline

At baseline, tumor lesions/lymph nodes will be categorized 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 short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in 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 non-measurable lesions. Lesions considered non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

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**:

4. 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.
5. ‘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 patient, these are preferred for selection as target lesions.

- **Lesions with prior local treatment:**

6. 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 13.

Table 13 - 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 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 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 below 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 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 patients 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 patient 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 preexisting 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 patient 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:

A) Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

B) 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 preexisting 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 14 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

Table 14 - Response in patients 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

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

When patients have non-measurable (therefore non-target) disease only, Table 15 is to be used.

Table 15 - Response in patients 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

Abbreviations: 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 patient 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 patients 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 patient with time point responses of PR-NE-PR as a confirmed response.

Patients 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 patients 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 (23).

10.8 APPENDIX 8: COUNTRY-SPECIFIC REQUIREMENTS

It is expected that sites in China will enroll 15% of the global study population. If enrollment of this proportion of the study participants at Chinese sites is not achieved at the time of completion of global enrollment, randomization may remain open for sites in China in order to achieve approximately 15% of the total study population.

10.8.1 Safety run-in in China

At the time of Protocol Amendment02 submission, there is no experience with tusamitamab ravtansine in Chinese patients. However, based on available data, no ethnic difference in the tusamitamab ravtansine safety profile is expected between Chinese and non-Chinese patients.

A safety run in step will consist in the sequential treatment of 6 patients with tusamitamab ravtansine (ie, approximately 12 randomized patients); none of the first 3 patients of tusamitamab ravtansine arm will be treated for first dose on the same day. The safety review will occur when 6 Chinese patients have been exposed to-tusamitamab ravtansine and completed a minimum of 2 cycles duration (~4 weeks) of treatment. If 0-1 of 6 evaluated patients had treatment related AESI or treatment related AE leading to the treatment discontinuation, enrollment will continue in China. Otherwise, enrollment will be on-hold in China and further safety and PK assessment will be performed

10.8.2 PK assessment in China

In the first 12 patients in China treated with tusamitamab ravtansine after implementation of the Protocol Amendment02, blood samples will be collected for measurement of plasma concentrations of tusamitamab ravtansine as listed in Table 16. These PK concentrations will be used to calculate, in these patients, the pharmacokinetic parameters using non-compartmental methods.

PK samples from subsequent participants treated with tusamitamab ravtansine in China as well as from participants enrolled and treated with tusamitamab ravtansine before implementation of the Protocol Amendment02 will be collected as described in Section 8.5.

Instructions for the collection and handling of biological samples will be provided by the Sponsor in a separate document. The actual date and time of each sample will be recorded. These samples will be tested by the Sponsor's designee.

Table 16 - PK sampling schedule for 12 tusamitamab ravtansine treated patients in China

Cycle	Day	Sampling timepoints	Time window allowance
Cycle 1	Day 1	SOI	Within 48h before SOI
		EOI	±10 min around the EOI
		EOI+4h	±30 min
	Day 2	24h	±5 h
	Day 3	48h,	±10 h
	Day 4	72h	±10 h
	Day 8	168h	± 24 h
Cycle 2		SOI	Within 24h before SOI. Sample must be collected even if the patient is not administered with tusamitamab ravtansine at this visit

Cycle	Day	Sampling timepoints	Time window allowance
Cycle 3		SOI	Within 24h before SOI
		EOI+1h	±10 min
Cycles 4, 5, 6 and 7		SOI	Within 24h before SOI
From Cycle 13		SOI every 6 cycles	Within 24h before SOI

EOI : end of infusion (ie, when the pump beeps before flush), SOI : start of infusion

10.8.3 Assessment of ATA, circulating CEA in China

ATA samples will be collected as described in Section 8.9, to assess the immunogenicity in Chinese patients. Circulating CEA samples will be collected at baseline and during treatment as described in Section 8.6.1, to assess circulating CEA as a potential pharmacodynamics biomarker of response to tusamitamab ravtansine treatment and as a potential impact on PK of tusamitamab ravtansine.

10.8.4 Circulating tumor DNA and germline DNA

Samples for Circulating tumor DNA and Germline DNA will not be collected in Chinese patients.

10.9 APPENDIX 9: CYP SUBSTRATES WITH NARROW THERAPEUTIC RANGE (NTR)

Table 17 - 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

10.10 APPENDIX 10: STRONG CYP3A INHIBITORS

Table 18 - 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 (GS-9350)	none	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	Diuretics	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

STRONG CYP3A INHIBITORS			
CYP3A inhibitors	**Precipitant therapeutic class**	**Victim (oral, unless otherwise specified)**	**AUC Ratio**
Potent CYP3A Inhibitors (yielding substrate AUC ratio >5)			
Ceritinib	Kinase Inhibitors	Midazolam	5.84
Ribociclib	Kinase Inhibitors	Midazolam	5.17
Josamycin	Antibiotics	Ivabradine	7.70
Tucatinib	Kinase Inhibitors	Midazolam	5.74

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 2021 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: PROTOCOL AMENDMENT HISTORY

Five previous amendments were created. The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

10.11.1 AMENDED PROTOCOL 05 (18-OCT-2022)

This amendment 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 because it may impact the scientific value of the study.

OVERALL RATIONALE FOR THE AMENDMENT

Based on regulatory authority input, the nonsquamous non-small-cell lung cancer (NSCLC) treatment landscape, and Sponsor considerations, assumptions for calculation of sample size for analysis of the primary endpoint, overall survival (OS), are being revised, prompting decreases in proposed sample size from 554 to 450 participants and number of OS events at final analysis from 452 to 363 deaths while maintaining adequate statistical power for the final analysis of OS. Final progression-free survival (PFS) analysis will be conducted with a lower number of events than initially planned, while maintaining adequate statistical power for this final analysis. In addition, the interim analysis (IA) of PFS at 60% information fraction has been removed, as it is anticipated that data will be immature at this time, leaving the final analysis of PFS as the only planned analysis of PFS. Due to the earlier timing of the cut-off date for IA for OS concurrent with the final PFS analysis, at 50% of the anticipated total OS events, an additional IA for OS was added at 80% OS information fraction, when enrollment is expected to be complete.

As the futility rules for OS became too stringent following the above-mentioned changes, the beta-spending function for OS futility analysis was replaced by a criterion based on observed hazard ratio (HR), using a criterion based on observed HR similar to that planned with the initial design.

In the anticipated case that analysis of PFS shows a statistically significant advantage of tusamitamab ravtansine over docetaxel, participants randomized to docetaxel may be expected to benefit from the access to treatment with tusamitamab ravtansine after objective disease progression. This amendment therefore includes provisional implementation, under conditions detailed in the protocol, of a crossover tusamitamab ravtansine treatment phase for participants with documented progressive disease during or after the docetaxel treatment.

Beside these changes, further modifications to protocol wording as detailed in the Summary of Changes table were implemented.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis, 1.2 Schema; 9.2 Sample size determination, 9.5 Interim analyses	The total sample size, the number of OS events at the interim and final analyses of OS, and the corresponding statistical power and efficacy boundaries were revised.	To reflect the revised OS hypothesis.
1.1 Synopsis, 1.2 Schema; 9.2 Sample size determination	The number of participants to be randomized to each arm was updated from 277 to 225	To reflect the revised sample size.
1.1 Synopsis, 4.4 End of study definition, 9.2 Sample size determination, 9.4 Statistical analyses; 9.5 Interim analyses; 9.6 Multiplicity	The estimated cut-off dates and timelines for the final analysis of progression-free survival (PFS) and interim and final analyses of overall survival (OS) were updated.	Timelines were adjusted based on the reduced total sample size, the addition of the 80% OS interim analysis, and the current enrollment curve.
1.1 Synopsis, 4.4 End of study definition; 9.2 Sample size determination; 9.4 Statistical analyses; 9.5 Interim analyses; 9.5.1 Data Monitoring Committee (DMC); 9.6 Multiplicity	Removed PFS IA at 60% information fraction	Based on regulatory authority input, PFS data are anticipated to be immature at this cut-off date
1.1 Synopsis, 9.2 Sample size determination	Estimated rate of dropout for sample size calculation was increased to 3%	Adjustment to match observed dropout rates
9.2 Sample size determination	Rounded enrollment assumptions from 11.89 participants/month to 12 participants/month, and added alternative cut-off date projections based on 10 participants/month	To provide estimated cut-off date projections that better reflect observed enrollment rates
1.1 Synopsis, 9.2 Sample size determination, 9.5 Interim analyses	The beta-spending function planned to be used for the assessment of futility at the time of the first IA of OS was removed and replaced by a rule based on observed OS HR; added Table 7.	To maintain the same futility criterion based on observed HR as initially planned

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis; 9.2 Sample size determination; 9.4.1.1.2 Overall survival; 9.5 Interim analyses; 9.6 Multiplicity	The number of OS events at the 50% information fraction IA of OS was updated, and a new IA of OS at 80% information fraction was added	Based on a new strategy for interim analyses of OS and adjustments to the total number of events for the final OS analysis, the estimated number of events at the 50% information fraction IA of OS changed, and a second IA of OS was added.
1.1 Synopsis, 1.2 Schema; 1.3 Schedule of activities newly specified 1.3.1 Main phase and new 1.3.2 Crossover phase; 3 Objectives and endpoints; new 4.1.2 Crossover phase; 5.1 Inclusion criteria; 5.2 Exclusion criteria; 6.6 Dose modification; 9.3 Populations for analyses; 9.4.1.3 Analysis of exploratory efficacy endpoints; minor wording changes throughout document	Subsections added under Section 5.1 and 5.2 to define minimal entrance criteria for allocation to crossover treatment phase Specified that dose reductions/delays and retreatment criteria for crossover participants would be according to the same rules for participants in the main study phase. Added text in other sections, wherever needed, describing provisional crossover treatment phase, required assessments and analyses of safety and efficacy for crossover treatment participants; wording adjusted as necessary throughout to reflect distinction between main study phase and newly added crossover phase.	To reflect addition of new provisional tusamitamab ravtansine crossover treatment phase for participants who progress during or after docetaxel treatment in the main study phase
2.1 Study rationale	Updated data based on results for nonsquamous NSCLC patients in first-in-human study TED13751	To provide data from a study of tusamitamab ravtansine as a treatment in this patient population
2.3 Benefit/risk assessment	Added cardiotoxicity to potential risks	To reflect the current safety information in the Investigator Brochure, edition 9.
3 Objectives and endpoints	Tertiary objectives and endpoints were added to specify safety and efficacy analysis for participants in the tusamitamab ravtansine crossover treatment phase	To reflect anticipated analyses for the crossover population.
5.1 Inclusion criteria I03; 4.1 Overall design; 8.8.1 CEACAM5 expression in tumor tissue samples	Reduced required number of slides from 7 to 5	To expand the number of eligible participants, as the sample size required for validation of the assay for tumor CEACAM5 expression was met
5.2 Exclusion criteria	Exclusion criterion E17 was modified to decrease minimally required eGFR (MDRD) for participants with elevated creatinine from 60 mL/min to 50 mL/min; additionally, participants with elevated creatinine but eGFR ≥50 mL/min/1.73 m^2 are now eligible.	As minimal urinary excretion of SAR408701 and its metabolites was observed in mice; population PK analysis from clinical study TED13751 did not identify creatinine clearance as a significant covariate for PK of SAR408701, DM4, or Me-DM4; and no major renal safety concern has been observed in clinical studies with tusamitamab ravtansine; modification of requirements to broaden the study population to include participants with minimal renal impairment is appropriate.

Section # and Name	Description of Change	Brief Rationale
8.5 Pharmacokinetics	Added PK and ATA sampling schedule Table 3	To clarify sampling times for the main study phase.
9.3 Populations for analyses	Clarified Screened population as those participants who signed screening informed consent	To simplify definition, as only those whose tumors meet CEACAM5 immunohistochemical criteria in prescreening are asked to sign screening informed consent
9.4.1.2.1.2 Time to deterioration in disease-related symptoms, time to deterioration in physical function, time to deterioration in role function	Modified description of analysis population and censoring rules for data analyses of time to deterioration in PRO endpoints	Clarification of how PRO data will be handled if data are missing or not evaluable.
10.8 Appendix 8: Country-specific requirements	Specified continuation of enrollment in China after the study cut-off date, if the minimum required sample size is not reached by the time global enrollment is complete.	To meet a local requirement for registration of tusamitamab ravtansine in China.
11 References	Added reference citations for presentations based on preliminary findings from Study TED13751	To provide further detail for study rationale
Throughout document	Minor typographical and grammatical corrections	To improve readability and consistency in the document

10.11.2 Amended protocol 04 (21-Jul-2021)

Amended protocol 04 (amendment 04) is considered to be nonsubstantial 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 because it does not significantly impact the safety or physical/mental integrity of participants or the scientific value of the study. The added interim analysis will be used as early assessment of safety and preliminary efficacy.

OVERALL RATIONALE FOR THE AMENDMENT

The main purpose of this amendment is to add an interim analysis on the PFS to occur when 60% of anticipated events (ie, disease progression or death) have been recorded.

The goal of this interim PFS analysis is to provide preliminary efficacy data. No predetermined stopping rule is to be applied to this interim analysis of PFS.

Regardless of this interim PFS outcome, the study will continue until the planned final analysis of PFS and then final analysis of OS, unless the interim analysis of OS at the time of final PFS analysis showed overwhelming efficacy or futility.

An external independent statistician will perform the unblinded interim analysis of PFS for the purpose of the DMC data review. Access to these data and analyses will be restricted to the DMC members and to limited personnel from the Sponsor involved in the submission if the analysis is positive and DMC recommends unblinding. DMC recommendation will be based on statistical criteria for PFS, as pre-specified in this protocol, and on benefit/risk considerations.

SAR408701 has been granted the INN name as tusamitamab ravtansine and throughout the document is replaced with the INN name.

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
Title page	Sponsor address added	Administrative update
1.1 Synopsis	Predicted cut-off dates for final PFS and OS analyses were modified. Number of PFS events at final analysis and corresponding power were also updated.	Based on the current enrollment curves and the adding of interim PFS analysis at 60% of information fraction
	Updated the number of patients treated in TED13751	Based on realization of the enrollment
4.1.1 Duration of the study period	Estimated duration of enrollment period updated from 40 to 44 months	Based on current projection
4.4 End of Study definition	New cut-off date for interim PFS analysis was added and timing of cut-off dates for final PFS and final OS analysis were updated	Based on current projection
5.2 Exclusion criteria	Typo error corrected for E01 as “Untreated brain metastases or history of leptomeningeal disease”	For clarity
9.2 Sample size determination	Section updated by adding new interim PFS analysis and assumption per current status. Timing of cut-off dates for final PFS and final OS analysis were updated	To reflect new interim PFS analysis and consider current status.
9.4 Statistical analyses	Planned cut-off dates are updated by adding cut-off dates for interim PFS and updating assumption for final PFS and final OS analysis	To reflect new interim PFS analysis and consider current status.
9.4.1.1.1 Progression free survival	Number of required events for interim PFS analysis added and significance levels at interim and final analyses are updated	To reflect new interim PFS analysis.
9.4.1.1.2 Overall survival	Erroneously missed OS interim analysis details are added to this section	Typo error correction.
9.5 Interim analyses	Section updated by adding details related to the interim analysis for PFS. Timing of cut-off dates for final PFS and final OS analyses were updated.	To reflect new interim PFS analysis and consider current status.
9.5.1 Data Monitoring	Section updated by adding interim analysis for PFS	To reflect new interim PFS analysis.

Section # and Name	Description of Change	Brief Rationale
Committee		
9.6 Multiplicity	Section updated and a table (Table 6) is added to detail PFS hypothesis testing. Previous Table 6 and all tables afterwards renumbered. Table 7 (former Table 6) is updated with current cut-off dates and estimations	For clarity and to reflect new interim PFS analysis and consider current status.
10.1.5 Committees Structure – Data Monitoring Committee (DMC)	Section updated by adding the interim PFS analysis	To reflect new interim PFS analysis
10.10 Appendix 10: Strong CYP3a inhibitors	Table updated with current up-to-date version	Version change on reference table
Throughout document	Added INN tusamitamab ravtansine to compound identifier	New INN issued
	Minor formatting and typographical updates	Editorial changes

10.11.3 Amended protocol 03 (20-Jul-2020)

This amended protocol 03 (amendment 03) is considered to be nonsubstantial 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 because it does not significantly impact the safety or physical/mental integrity of participants or the scientific value of the study.

The main purpose of this amendment is to clarify protocol wording; in particular, to clarify the inclusion criteria regarding prior anticancer therapies. To ensure a homogenous study population limited to a single line of prior chemotherapy in advanced setting, the wording on inclusion criterion I02 has been modified, and a new exclusion criterion E25 added.

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
1.1 Synopsis (Objectives and endpoints), Section 3 Objectives and endpoints	Disease related symptoms and definition of Time to Deterioration added for health-related quality of life endpoint	For clarity
1.2 Schema	Wording added to footnote a as below "a … Patients who have additional tumor tissue samples available during the prescreening phase may be re-assessed for CEACAM5 expression level; the most recent tissue sample assessed for CEACAM5 expression will be used to determine eligibility of patients for screening."	To allow re-assessment for CEACAM5 expression in case a patient had an additional tumor tissue sample available
1.3 Schedule of activities (SOA)	Clarification added that height is measured only at screening visit, before the IRT call	For clarity

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of activities (SOA); 10.2 Table 8	"HBsAgV & HCV serology" is updated as HBV & HCV serology; specific HBV serology also noted in Table 8	For consistency between protocols in study schedule terminology
1.3 Schedule of activities (SOA)	Footnote b was updated to clarify that time windows are based on first infusion	For clarity
5.1 Inclusion criteria	Criterion I02 further modified	For clarity
5.1 Inclusion criteria	I06 criterion modified as: -Wording added to remind investigator regarding recommendation of sperm conservation for docetaxel	For clarity to reflect the docetaxel label.
	- To cover both men and women, highly effective" deleted from section specifically for male patients and added to the first sentence of criterion	Typographical error corrected, as this wording had been erroneously added to the section pertaining solely to men instead of the section for both sexes
5.2 Exclusion criteria	Criterion E01 updated to define assessment imaging window as "at least 4 weeks after CNS directed treatment and at least 2 weeks prior to first administration of study intervention."	To clarify the timing of required confirmatory scan for non-progression and also to allow patients diagnosed with brain metastasis to be enrolled with prolonged screening window
5.2 Exclusion criteria	E25 criterion added	Added as supportive criterion for clarity on I02 criteria
5.4 Screen failures	Section modified to allow prolonged screening period for temporary screen failure reason and detail the condition requiring screen failure and rescreening process.	To reflect and define operational process
6.5 Concomitant therapy	Details added for bone-targeted treatments; corrected link to Appendix 9 (Section 10.9)	To ensure standardization across studies; typographical correction
7.1.2 temporary discontinuation	Section updated to include details of guidance in case of regional or national emergency; link to new Appendix 12	As guidance for standardization across studies
Section 8	Information regarding measures in case of temporary discontinuation added; link to new Appendix 12 detailing changes to procedures in the case of regional or national emergency	
8.2.2 Specific ocular tests	Text added to allow omitting Schirmer's test during treatment period and follow-up, if considered not required per ophthalmologist.	Test is not routinely done in some sites
8.2.3 Vital signs	Pulse measurement deleted	To correct typographical error
8.2.4 Electrocardiograms	"..(even cycles for SAR408701 and odd cycles for docetaxel)".. added "For the SAR408701 arm" added to clarify that end of infusion ECG is required only in SAR408701 arm	For clarity

Section # and Name	Description of Change	Brief Rationale
8.2.5 Clinical Safety laboratory assessment	added "..ie ALT, AST,ALP, total and direct bilirubin).." added to clarify the liver function test for weekly assessment Also, section updated to allow laboratory tests to be performed within 2 days before the IMP administration	For clarity Per operational need at site
8.3.7 Disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs	Sentence added to clarify that lack of efficacy is not reported as AE/SAE as part of efficacy analysis	For clarity on related section
8.5 Pharmacokinetics	Section updated to add time windows for each PK sample	For clarity
8.7 Genetics	Below wording added to clarify that genetic tests are mandatory "..to perform the required genetic tests (unless not allowed by local authorities).."	For clarity
8.9 Immunogenicity	Wording added to clarify that ATA samples are collected at the same time with PK samples	For clarity
9.4.1.2.1.2 Time to deterioration in disease-related symptoms, time to deterioration in physical function, time to deterioration in role functions	Section updated to detail HRQOL endpoints and statistical analysis	For clarity
9.4.3 Other analysis	Wording added related to analysis on impact of the regional or national emergency situation	For clarity
10.1.3 Informed consent process	Section updated to reflect prolonged screening window and requirement of reconsent in case of rescreening.	For clarity
10.1.3 Informed consent process	"..and sample for cfDNA analysis." deleted as cfDNA are mandatory assessment unless not allowed by local authorities	For clarity
10.2 Clinical Laboratory tests	Erroneously added "Non-fasting" deleted to allow site to follow the correct process	To correct typographical error
10.3 Adverse events: definitions and procedures for recording, evaluating, follow-up and reporting	Last bullet removed from Events meeting the AE definition	Removed as it was repeated text as in above bullet
10.8.2 PK assessment in China	Table 13 updated with time window for C1D1 predose as within 48h, Table updated by adding column with study days for cycle 1 sampling and creating a separate row for each 72h samples (previously on same row with 48h sample)	To allow flexibility to site to get sample with baseline laboratory assessment For clarity
10.12 Contingency measures for a regional or national emergency that is declared by a governmental agency	New appendix added to detail contingency measures for a regional or national emergency	To harmonize across sites actions taken in response to regional or national emergency.
Throughout	Minor editorial, typographical error corrections and standardization of wording.	For Clarity

10.11.4 Amended protocol 02 (13-Dec-2019)

This amended protocol (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 amendment 02

The protocol has been amended to add one additional ECG assessment at the approximate time of SAR408701 C_{max} in the SAR408701 arm for the purpose of more intense cardiac safety assessment. In addition, the protocol is updated to clarify the management of patients who were exposed to SAR408701 after an ocular event.

At the time of amendment 02, there is no experience with SAR408701 in Chinese patients. No ethnic difference in SAR408701 safety profile is expected between Chinese and non-Chinese patients. The protocol is updated to add a safety run-in assessment phase and pharmacokinetic run-in phase for the SAR408701 arm in Chinese patients to secure safety as well as to obtain safety and pharmacokinetic data as detailed below.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.1. Synopsis Statistical consideration	Paragraph for Pharmacokinetic population modified as " this population will include safety participants who have actually received at least one dose or a part of a dose of SAR408701 with at least one concentration post baseline with adequate documentation of dosing and sampling dates and times. "	For clarity
1.3 Schedule of Activity	The X added for 12-Lead ECG before the infusion at Cycle 1 and for blood chemistry for EOT visits	Correction of typo errors
1.3 Schedule of Activity	The X added for 12-Lead ECG after EOI at Cycle 1.	EOI assessment added for collection of the 12-Lead ECG at the estimated SAR408701 C_{max}
1.3 Schedule of Activity	Footnote a – PD1 updated as PD-L1 and typo error corrected Footnote d – "On-site" wording deleted for follow-up visits.	Typo error correction To allow phone contact in case the patient's general condition is not suitable for on-site visit
3 Objectives and Endpoints	Secondary endpoint definition is updated by adding "… derived from Overall Response (OR)…."	For clarity. Best Overall Response (BOR) will be programmatically derived by sponsor following RECIST 1.1 algorithm from OR determined by the IRC per RECIST 1.1.

Section # and Name	Description of Change	Brief Rationale
5.1 Inclusion	I06 – The duration of contraception for male participant updated as 6 months instead of 4 months	For clarity, to cover docetaxel related fertility recommendation as a requirement in some countries
5.2 Exclusion Criteria	E17 updated as "[…or 1.0 – 1.5x ULN with eGFR < 60mL/min/1.73m^2 as estimated using aMDRD formula" by replacing CrCL with eGFR.	Typo error correction, for clarity to reflect formula
Study Intervention	Premedication for docetaxel arm: Text deleted "an iv histamine H1 antagonist given as predose and"	To reflect current docetaxel labels
8.2.4 Electrocardiograms	The addition of the 12-Lead ECG after EOI at Cycle 1 only. Below wording added: In addition to before the infusion assessment, "Single 12-lead ECG is also required within 30 minutes after the EOI (End Of Infusion) at Cycle 1 only (see section 1.3)."	The collection of the 12-Lead ECG at the time of estimated SAR408701 Cmax.
8.2.6 Guideline for management of adverse event	Section updated by adding below text: "The docetaxel label should be followed for management of docetaxel specific adverse event if otherwise not specified in the protocol."	For clarity
8.2.6.2 Ocular toxicity	Section updated by adding below texts: "...Then patient should be followed with ocular exam (Slit Lamp and visual acuity) at each cycle until total resolution of the event …." ….. "After resuming study treatment, the patient who had Grade ≥2 keratopathy/keratitis should be followed with standard ocular exams (ie Slit Lamp examination under dilatation and Visual acuity) by every two cycles, even with no reported symptoms. If no recurrent event during the next four cycles, then regular follow-up (ie, symptom assessment at each visit with standard ocular exam in case of any ocular sign/symptom) is applied."	For clarity, as a guidance on safety management and follow-up of the patient
8.2.6.3 Management of anemia	Hemoglobin unit was updated from mg/dL to g/dL Text added "Current clinical guidelines should be followed for management of anemia" The text deleted "Cycle delays or modifications should be compliant with Appendix 10.4.	Typo error For clarity Typo error
8.2.6.5 Liver function tests	Grade 4 updated as Grade ≥3	Typo error
8.2.6.6 Peripheral neuropathy	"Section added to detail recommendation on peripheral neuropathy	For clarity, as a guidance on safety management and follow-up of the patient
8.2.6.7 Gastrointestinal toxicity	Section added to detail recommendation on gastrointestinal toxicity	For clarity, as a guidance on safety management and follow-up of the patient

Section # and Name	Description of Change	Brief Rationale
8.3.1 Adverse Event of Special Interest	Keratopathy updated as "keratopathy/keratitis" Grade 4 liver enzyme increase modified to Grade ≥3	For clarity to cover drug induced keratitis Typo error
8.5 Pharmacokinetics	Section updated by adding below text: "For patients randomized to the SAR408701 arm" Section was updated to add PK samples every 6 cycles after Cycle 7 (ie, at pre-dose Cycles 13, 19, 25,…).	To collect time-matched PK samples with immunogenicity samples beyond Cycle 13.
8.9 Immunogenicity	Section updated by adding below text: "For patients randomized to the SAR408701 arm"	For clarity
9.3 Populations for Analysis	Definition of Intent to Treat (ITT) population is updated that it will be based on allocated treatment kit numbers in the IRT	For clarity
	Pharmacokinetic section updated by adding below text: with adequate documentation of dosing and sampling dates and times.	For clarity
10.2 Appendix 2: Clinical Laboratory Tests	Table 8 footnote a, last sentence wording has been modified as below: All events of grade ≥3 AST/ALT increase should be reported as adverse events of special interest (AESI).	For consistency
10.4 Appendix 4: Recommended Supportive Care and/or Dose Modification Guidelines for Drug-Related Adverse Events	*Ocular toxicity:* The supportive column was revised as merged for Grade 2 and Grade 3 and updated as below: Standard ocular examination weekly until resolution. 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, as detailed in Section 8.2.6.2. 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. *Febrile neutropenia*: Below paragraph added to Management of dosing column for SAR408701 under Grade 4 Life-threatening consequences: "1st episode: administer next cycle at reduced dose and administer G-CSF or definitively discontinue 2nd episode: definitive discontinuation"	For clarity on safety management

Section # and Name	Description of Change	Brief Rationale
10.4 Appendix 4: Recommended Supportive Care and/or Dose Modification Guidelines for Drug-Related Adverse Events	Below paragraph added to Management of dosing column for Docetaxel under Grade 4 Life-threatening consequences: "1st episode: administer next cycle at reduce dose and administer G-CSF or definitively discontinue 2nd episode: definitive discontinuation" Grade 3 changed to Grade ≥3 on Supportive Care Guideline Column *Peripheral Neuropathy:* Section added for recommendation on dose modification and supportive care for peripheral neuropathy	For clarity on safety management
10.8 Appendix 8: Country Specific Requirement	Section updated to detail safety run-in step and pharmacokinetic run-in with 12 SAR408701 treated participants with full PK sampling at Cycle 1 for China.	To secure safety and well-being of Chinese patients as well as to obtain safety and pharmacokinetic data in EFC15858 study.

10.11.5 Amended protocol 01 (27-Sep-2019)

This amended protocol (amendment 01) 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 treatment landscape in nonsquamous, non–small-cell lung cancer is rapidly evolving with the integration of immune check point inhibitors (ICI) that are more and more widely marketed and are becoming fully part of the therapeutic strategy, used either in front line metastatic setting in combination with platinum-based chemotherapy or as monotherapy, eg, after relapse of chemotherapy (or targeted therapy for patients having genetic mutation of their cancer). In this context and to have a homogeneous patient population, the study is amended to include only patients who have received prior treatment with one platinum-based chemotherapy and an anti-PD-1/PD-L1 monoclonal antibody. Based on this modification, a stratification factor related to prior ICI treatment was adopted, specifically, whether prior ICI treatment was given in combination with chemotherapy or sequentially as monotherapy.

In order to provide additional evidence of clinically meaningful efficacy, timing of the final progression free survival (PFS) analysis was amended to be performed at the time when 50% of OS events have occurred. This will allow for OS data to be more robust than in the original plan at the time of the final PFS analyses.

With further analyses of availability of validated scales by country and the operational feasibility feedbacks, a reassessment of the Health Related Quality of Life (HRQOL) scales to be administered in the study was performed. It has been considered to adapt HRQOL related sections with perspective of focusing on secondary endpoints only and deleting tertiary endpoints. This is mainly in the context of unavailability of culturally validated translation of NSCLC SAQ and

VisQoL scales in all countries targeted for the study, as well as the limitation of interpretability of PRO data in an open label study design. Disease related symptoms will be captured from EORTC QLQ-LC13 and the impact of the ocular toxicity will be gathered by analyses of overall safety impact, general physical and role functional quality of life assessment of the EORTC QLQ-C30 as well as analysis of ocular symptoms and adverse events.

Additional modification implemented for clarification around protocol wording, as detailed on summary of changes table below.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Title page	"in previously treated" added to Short title	To reflect original protocol
1.1 Primary objective; 3.0 Table 1	The "doublet" and "if indicated" wording deleted	To reflect the study population
1.1 overall design; 1.2 footnote b; 4.1 Overall design;	Stratification factor related to prior ICI treatment updated as Sequential versus combination with chemotherapy instead of Yes versus No	To reflect the study population. This criterion considered as best reflect the study population in terms of prior PD-L1 expression level.
1.1 Statistical considerations - sample size consideration	Final Overall Survival analysis assumption updated as 452 events instead of 446 with consideration of one Interim analysis (IA) for Overall survival (OS) when 50% of events (226 deaths) will be observed. Final Progression Free Survival analysis assumption updated at the time of 50% of OS event as 275 events instead of 221 events with log-rank test at one-sided 0.01 level and power of approximately 95.5% Timelines of final PFS analysis updated as 31 months instead of 26 months and final OS analysis at 51 months instead of 50 months after first participant in the study.	Updated to reflect new design of final PFS analyses at the time of 50% of OS events instead of 38% of OS events, with consideration of achieving more mature OS interim analysis at the time of final PFS analysis.
1.1 Statistical considerations Analysis of secondary efficacy endpoints	Below sentence added to HRQOL related analysis of secondary endpoints Details of subscales from EORTC QLQ-LC13 and EORTC QLQ-C30 and list of items to be used for disease-related symptoms, physical function and role function will be provided in the statistical analyses plan	For clarity
1.1 Interim analysis, statistical considerations	Timing of OS interim analysis updated as 50% of events (ie, approximately 226 deaths) instead of about 38% (ie. 169 deaths)	To reflect new statistical design as detailed above

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activity	The X added to prescreening for Demography, medical/surgical/disease history and smoking history	For consistency
	X deleted from C1D1 assessment of serum pregnancy test, 12-Lead ECG and ocular tests	To prevent frequent tests
	NSCLC SAQ and VisQoL scales deleted from ePRO row	
	Footnote e added for ePRO related description.	For clarity
	Sentence added to footnote c: C1D1 hematology, blood chemistry and coagulation tests may be omitted if baseline test performed within 7 days are normal. If baseline test are abnormal should be repeated within 2 days of first study intervention.	
3 Objective and Endpoints	Tertiary/exploratory – Two HRQOL related endpoints were deleted as NSCLC SAQ and VisQoL deleted	As described on Amendment rational.
	Tertiary- "CEACAM5 pattern" is added to the endpoint of last objective	For analysis of CEACAM5 pattern beside CEACAM5 expression level
3.1 Appropriateness of measurements	This sentence deleted: The NSCLC-SAQ (SAQ) is an FDA qualified clinical outcome assessment to measure symptoms of non-small cell lung cancer.	To reflect amendment
4.4 End of Study Definition	Timelines of Final PFS and interim OS analyses updated as 31 months instead of 26 months and final OS analysis 51 months instead of 50 months	For consistency to reflect new statistical design
5 Study population	I02 criterion updated with	
	- subsection bullets changed from i, ii, iii to a, b, c	For clarity
	- deletion of sentence linked to waiver on prior ICI treatment	To reflect new restriction of participant population to previously ICI treated patients
	- addition of below sentence to bullet i to allow prior refractory population to be enrolled	For clarity
	"Patient who had adjuvant / neoadjuvant treatment and relapsed as metastatic disease during or within 6 months of treatment will be considered as first line treatment"	For clarity
	- Bullet iii updated	For clarity
	E01 updated as "Untreated brain metastases and history of leptomeningeal disease. […]" and corticosteroid washout decreased to 2 weeks from 4 weeks	Typo error
	E04 Definition of active hepatitis B updated with correction of or instead of and as "…. either positive HBsAg **or** positive hepatitis B viral DNA test above the lower limit…"	
	E06 Updated as "Unresolved corneal disorders or any previous corneal disorder that considered by ophthalmologist that patient may have risk of drug induced keratopathy.	For clarity per feasibility feedbacks

Section # and Name	Description of Change	Brief Rationale
6 Study intervention; 6.5 Concomitant therapy	Premedication of docetaxel updated as "…(eg, 8 mg BID dexamethasone or equivalent corticosteroids).."	To reflect possibility of equivalent corticosteroid use per site process.
	Use of prophylactic erythropoietin limited to "first cycle" rather than "first two cycles"	To take into account docetaxel and use of G-CSF
8 Study assessments and procedures	Specified that, with the exception of age, demographic data (gender, race, ethnicity, smoking status); histology and stage at diagnosis; and biomarkers [tumor mutation status including PD-1 expression, circulating CEA] when available) collected during prescreening will be used for analyses of baseline demographic and disease characteristics. Age, disease extent at study entry, and previous antitumor therapy (type, start and end dates, reason for discontinuation, and response to the therapy) and change in smoking history will be collected at Screening, and will be considered as baseline data.	To clarify the use of prescreening data to prevent double data entry
8.2.6.2 Ocular toxicity;	Clarified that artificial tears are recommended only for participants treated with tusamitamab ravrtansine.	For clarity
8.2.6.3 Management of anemia	Section updated to allow erythropoietin use after the first cycle, instead of after the first 2 cycles.	As guidance for management of participant safety
8.5 Pharmacokinetics	Removed duplicated statement referring to nonlinear mixed-effects modeling for population PK analysis.	To reduce repetition
8.11 Patient Reported Outcome	The window to fill electronic patient report outcomes (ePROs) at pre-dose on Day 1 of Cycle 1 was changed from (up to within 7 days) to (up to within 3 days)	Adapted to reflect randomization window to ensure data collected in randomized participant only
8.11.3 VisQoL	Section was deleted	To reflect amendment
8.11.4 NSCLC SAQ	Section was deleted	To reflect amendment
9.2 Sample Size Determination	Section updated to reflect new statistical design on timing of final PFS (with assumption of 275 PFS events) and OS analysis at 31 months at the time of 50% of OS events and final OS analysis with a total of 452 deaths	To reflect amendment as detailed on amendment rational
9.2 Sample Size Determination	Phrase below: "achieve 554 randomly assigned to study intervention" replaced with "for CEACAM5 status, of whom 650 patients will be screened to achieve 554 randomized patients with estimated failure rates of 80% for pre-screening and 15% for screening"	For clarity

Section # and Name	Description of Change	Brief Rationale
9.4 Statistical analyses	Estimated cut-off dates updated	To reflect amendment
9.4.1 Table 4	QoL SAQ, VisQoL deleted from Exploratory endpoint	To reflect amendment
9. 4.1.1.1 progression free survival	Censoring rules updated: For patients alive without PD at the COD, PFS will be censored at the date of the last valid assessment before the COD without taking into account the response of the tumor assessment after the COD if any. PFS will not be censored at the COD anymore	To avoid to introduce informative censoring and bias in the estimated treatment effect in case of imbalance of informative censoring between arms and to not favor the arm with more informative censoring
9.4.1.1.2 Overal survival	Text added “The cut-off date for the final analysis of OS will be the date when 452 deaths are observed	To clarify and to reflect amendment
9.4.3 Other Analyses	Text added: “The results of the population PK analysis will be presented separately from the main clinical study report (CSR).”	For clarity
9.5 Interim Analyses	Section updated with new statistical assumption	To reflect amendment
9.5.1 DMC	Below wording deleted “and have completed at least 9 weeks after first study intervention”	For clarity
9.6 Multiplicity	Below sentence updated “With 275 PFS events at final analysis the study has ~98% power for detecting a HR of 0.615 at one – sided alpha 0.02485” Table 6 updated to reflect new statistical assumptions	To reflect amendment
10.2 Clinical laboratory test	Below sentence added as footnote to Table 8 “Bicarbonate may be omitted at countries where its assay is not performed as part of the routine chemistry panel."	Based on feasibility feedback, in countries where routine venous blood blood chemistry assay is not used for this assessment
10.4 Recommended Supportive Care	Ocular toxicity; Definition of grades was updated with NCI CTCAE V5.0 wording	For clarity
10.5 Contraception	Section updated to allow up to 1 year of data collection on status of child.	To allow further data collection on baby of a female participant or a partner of a male participant in case of a need per PV requirement.
Throughout	Minor editorial, typographical error corrections and standardization of wording.	For Clarity

10.12 APPENDIX 12: CONTINGENCY MEASURES FOR A REGIONAL OR NATIONAL EMERGENCY THAT IS DECLARED BY A GOVERNMENTAL AGENCY

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).

As the situation may evolve differently by country, by region, or by site, each site should define its business continuity plan, and inform the Sponsor of its plan as early as possible. Some guidance to be considered in formulating a contingency plan during a regional or national emergency is provided in this section.

10.12.1 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 for only those participants who have enough archival samples a remote prescreening ICF process compliant with country/site requirements.

The process should be compliant with accepted principals of patients' rights and global, national, and local regulatory requirements. Requireed 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, SAR408701 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 email (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.

10.12.2 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 judgement 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; no protocol waiver is acceptable. Remote signature of main study ICF is not acceptable in any circumstance.

10.12.3 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, re-initiation) of the IMP can occur only once the Investigator has determined, according to his/her best judgement, that the contribution of the IMP(s) to the occurrence of the epidemic event (eg, COVID-19) was unlikely.

During a regional or national emergency due to pandemic (eg, COVID-19), the Investigator's choice, based on a benefit–risk assessment, to initiate prophylactic G-CSF treatment at Cycle 1 for a patient in the docetaxel arm should be considered acceptable. The Investigator's decision to initiate G-CSF should be detailed in the source data and reported on eCRF.

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.

10.12.4 Study procedures

Depending on site status, if needed, Cycle 1 and Cycle 2 weekly safety laboratory assessment (hematology [differential WBC] 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 patient home, or via sampling at patient's home.

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 capacitiy 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 to be sent to IRC.

10.13 APPENDIX 13: ABBREVIATIONS

AESI:	adverse event of special interest
CEACAM5:	carcinoembryonic antigen-related cell adhesion molecule 5
CI:	confidence interval
CR:	complete response
DM4:	maytansinoid derivative 4
DMC:	data monitoring committee
DOR:	duration of response
ECOG:	Eastern Cooperative Oncology Group
EOI:	end of infusion
EOT:	end of treatment
ePROs:	electronic patient report outcome
FDG-PET:	fluorodeoxyglucose-positron emission tomography
FFPE:	formalin-fixed paraffin embedded
FPI:	first patient in
FSH:	follicle stimulating hormone
GHS/QoL:	global health status/quality of life
HRQOL:	health-related quality of life
HRT:	hormonal replacement therapy
ICF:	informed consent form
ICH:	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IHC:	immunohistochemistry
IMP:	investigational medicinal product
IRC:	radiological review committee
IRT:	interactive response technology
ITT:	intent to treat
IV:	intravenous
NCI-CTCAE:	National Cancer Institute Common Terminology Criteria for Adverse Event
NE:	not evaluable
NIMP:	non investigational medicinal product
NSCLC:	non small cell lung cancer
ORR:	objective response rate

OS:	overall survival
PD:	progressive disease
PD1/PDL1:	programmed death 1/ programmed death ligand 1
PF:	Physical function
PFS:	progression free survival
Q2W:	every 2 weeks
Q3W:	every 3 weeks
RF:	Role function
RoW:	Rest of the World
SAE:	serious adverse event
TEAE:	treatment-emergent adverse event
TTD:	time to deterioration
WOCBP:	woman of childbearing potential

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