AMENDED CLINICAL TRIAL PROTOCOL 02

Protocol title:	**Open-label, single-arm trial to evaluate antitumor activity, safety, and pharmacokinetics of tusamitamab ravtansine (SAR408701) used in combination with ramucirumab or ramucirumab and pembrolizumab in metastatic, non-squamous, non-small-cell lung cancer (NSQ NSCLC) patients with CEACAM5-positive tumors, previously treated with platinum-based chemotherapy and an immune checkpoint inhibitor**
Protocol number:	**ACT16525**
Amendment number:	**02**
Compound number (INN/Trademark):	**SAR408701 tusamitamab ravtansine/Not applicable**
Study phase:	**Phase 2**
Short title:	**Tusamitamab ravtansine (SAR408701) in combination with ramucirumab or ramucirumab and pembrolizumab in pretreated patients with NSQ NSCLC (CARMEN-LC04)**
Sponsor name: **Legal registered address:**	**Sanofi-Aventis Recherche et Développement** **1 Avenue Pierre Brossolette,** **91380 Chilly-Mazarin, France**
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According to template: QSD-002434 VERSION N°17.0 (26-NOV-2018)

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 02	All	20 December 2022, version 1 (electronic 2.0)
Amended Clinical Trial Protocol 01	All	12 November 2020, version 1 (electronic 1.0)
Original Protocol		10 December 2019, version 1 (electronic 1.0)

Amended protocol 02 (20 December 2022)

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

OVERALL RATIONALE FOR THE AMENDMENT

The purpose of this amendment is to add a new cohort of 6 to 12 patients to assess the safety and tolerability of a new combination of tusamitamab ravtansine (SAR408701) with ramucirumab and pembrolizumab given every 3 weeks (Q3W) to be further used in future clinical trials.

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 and short tittle	Modified title to add pembrolizumab	To reflect addition of a new cohort
Title and short title; Throughout the document	Added tusamitamab ravtansine INN name and SAR408701 replaced by INN name	The approved product name was added
List of Figures; 1.2 Schema	Added Figure 3c	To reflect addition of a new cohort
1.1 Synopsis; 2.1 Study rationale; 3 Objectives and endpoints, Table 3; 9.4.1 Efficacy analyses, Table 16; 9.4.2 Safety analyses, Table 17	Added objectives and endpoints specific to new cohort with the addition of pembrolizumab Added rationale to add pembrolizumab to the combination	To reflect addition of a new cohort
1.1 Synopsis, Intervention groups and duration; 4.1 Overall design	Added details related to triplet cohort with pembrolizumab, added 1.3.2	To reflect addition of a new cohort

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis, Study interventions; 6.1 Study interventions administered	Added details related to pembrolizumab and updated dose regimen of SAR408701 and ramucirumab for doublet and triplet cohort separately. Added Table 8 for triplet cohort	To reflect addition of a new cohort
1.1 Synopsis, 4.1 Overall design	Added DLT evaluation period Figure 2 and Figure 5 for Decision tree for triplet cohort for tusamitamab ravtansine, are newly added in Section 1.1 and 4.1, respectively	To reflect addition of a new cohort
1.3.2 Study Flow Chart - Triplet cohort	Added new flow chart specific to the triplet cohort with addition of thyroid function tests and changed dosage schedule to Q3W	To reflect addition of the new cohort
1.3.3. Pharmacokinetic/Anti-therapeutic antibody flow charts	Added new flow chart for the triplet cohort as 1.3.3.3 Triplet cohort	To reflect addition of the new cohort
2.3 Benefit/Risk Assessment	Added information regarding potential benefit of pembrolizumab and combination with tusamitamab ravtansine	To provide new information for the triplet cohort
5.2 Exclusion criteria	Added pembrolizumab related exclusion criteria E38 to E46 Added “or ≥2.5 mL” was added to E10 Added “arterial” thrombotic disorder to E08	To reflect addition of pembrolizumab For clarity For clarity
5.5 Criteria for temporarily delaying	Added paragraph to mention Appendix 11	To comply with new protocol template V8
6.1 Study Intervention administered	Added possibility to use PO premedication	For clarity
6.5.1 Treatments prohibited during study	Added duration for erythropoietin prohibition for triplet cohort	To reflect addition of the new cohort
1.1 Synopsis; 4.1 Overall design; 6.6.2 Triplet cohort, Table 10	Added new section with dose reduction for triplet cohort Table 2 and Table 6 are newly added in Sections 1.1 and 4.1, respectively	To reflect addition of the new cohort
1.1 Synopsis; 6.6.4 Dose adjustement/dose delay, Table 12; 10.4 Appendix 4: Recommended supportive care and/or dose modification guidelines for drug-related adverse events	Added pembrolizumab and dose modification for toxicity for the triplet cohort table	To reflect addition of the new cohort
7 Discontinuation of study intervention and participant discontinuation/withdrawal	Added cycle duration, study cut-off for primary ORR endpoint analysis for the doublet cohort and secondary ORR endpoint analysis for the triplet cohort	To reflect addition of the new cohort
8.1 Efficacy assessment	Specified tumor assessment frequency for the triplet cohort to 6 weeks	To reflect addition of the new cohort

Section # and Name	Description of Change	Brief Rationale
1.3.1 Study flow chart; 8.2.6.7 Proteinuria	Removed tests in case of proteinuria >500mg/24 hours The sentence: If proteinuria >500 mg/24 h: blood tests including haptoglobin, LDH, platelet count and schizocytes should be performed systematically. is removed from footnote k of Section 1.3.1 and from Section 8.2.6.7	Correction of error
8.2.7 Immune-related adverse reactions	Added new section with cross reference to Section 10.4 Appendix 4, for guidance for managing immune-related adverse reactions	To reflect addition of the new cohort
9.1 Statistical hypotheses	Add the triplet cohort statistical hypotheses	To reflect addition of the new cohort
1.1 Synopsis; 4.1 Overall Design. 9.2 Sample size determination	Added sample size for triplet cohort Added new section 9.2.3 Sample size for the triplet cohort	To reflect addition of the new cohort
9.3 Population for analyses Table 15	Clarified definition of screened population Definition for "DLT-Evaluable and Activity" is also updated	For clarity
9.4.1 Efficacy analysis Table 16; 9.4.1.1 Analysis of primary efficacy endpoint for the doublet cohort/Secondary efficacy endpoint for the triplet cohort	Added efficacy analysis for the triplet cohort	To reflect addition of the new cohort
1.1 Synopsis; 3 Objectives and endpoints Table 3; 9.4.1 Efficacy analyses Table 16; 9.4.1.2 Analysis of secondary efficacy endpoints for the doublet cohort	Added disease control rate as a secondary endpoint for doublet cohort	For efficacy analysis
1.1 Synopsis, 4.1 Overall design; 9.4.2 Safety analyses Table 17; 9.4.2.1 Analysis of primary safety endpoint	Added endpoint for the triplet cohort and DLT observation period	To reflect addition of the new cohort
10.2. Appendix 2: Clinical Laboratory Tests - Table 18	Added thyroid function assessment and parameters TSH, T3, FT4 for triplet cohort only	To reflect addition of the new cohort. Monitoring of thyroid function as per the established safety profile of pembrolizumab
10.3.1 Definition of AE	Removed symptomatic and/or requiring either corrective treatment or consultation in the criteria to consider lab abnormality as AE	To comply with Oncology standard
10.10 Appendix 10: Strong CYP3A INHIBITORS	Updated list of strong CYP3A inhibitors	To reflect the last version list
10.11 Appendix 11 referenced in Sections 5.5, 7.1.2, 8, 9.4.3 and 10.1.3	Modified to specify this section is only applicable for COVID-19	To comply with new protocol template V8.0
Appendix 12 (Section 10.12)	Moving summary of changes for amended protocol 1 to this section	Per Sanofi process

Section # and Name	Description of Change	Brief Rationale
10.13 Appendix 13 Abbreviations	Added Q3W, DCR abbreviations	To reflect addition of the new cohort
11 References	Added references	To reflect addition of the new cohort
Throughout	Correction of typographical errors and standardization of wording Cross reference numbers are updated, throughout the document.	For clarity

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol title:

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

Short title:

Tusamitamab ravtansine (SAR408701) in combination with ramucirumab or ramucirumab and pembrolizumab in pretreated patients with NSQ NSCLC (CARMEN-LC04)

Rationale:

Despite recent progress in the treatment of advanced NSCLC, there remains a need for effective new treatment at the time of disease progression. New cytotoxic treatments selectively targeted to tumor cells have the potential to improve efficacy while managing toxicity.

One feature that can be used to target some tumor cells is surface expression of carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5). High levels of CEACAM5 expression are observed in several epithelial tumors, including adenocarcinomas of the colon and stomach as well as NSQ NSCLC.

Maytansinoids are antimitotic agents that inhibit microtubule formation to act as very potent cytotoxic agents against tumor cell lines in vitro, with IC_{50} values 100- to 1000-fold more potent than conventional tubulin binding compounds, including docetaxel. Tusamitamab ravtansine (SAR408701) is an antibody to CEACAM5 conjugated to the cytotoxic maytansinoid agent, (DM4). Encouraging preliminary antitumor activity of tusamitamab ravtansine in patients heavily pretreated for NSQ NSCLC has been demonstrated in an ongoing study (TED13751). The balance of anticipated benefits and the reported risks of tusamitamab ravtansine identified in ongoing studies TED13751 and TCD15054 supports its continued clinical development, both as monotherapy and in combination regimens with chemotherapy and immunotherapy agents.

Ramucirumab (Cyramza®), a human IgG_1 monoclonal antibody that inhibits vascular endothelial growth factor receptor-2 (VEGFR-2), administered 10 mg/kg every 3 weeks (Q3W) in combination with docetaxel, is approved for the treatment of patients with metastatic NSCLC. Ramucirumab administered 8 mg/kg every 2 weeks (Q2W) also is approved for use as a single agent or in combination with paclitaxel for gastric cancer and hepatocellular carcinoma, and in combination with folinic acid/fluorouracil/irinotecan (FOLFIRI) for colorectal cancer (CRC). The choice of dosing schedule used in this study is supported by preliminary efficacy data from studies evaluating tusamitamab ravtansine 100 mg/m^2 Q2W and the ramucirumab 8 mg/kg Q2W

Immune checkpoint inhibitors (ICIs), administered alone or in combination with other anticancer therapies, have shown activity in treating a variety of tumor types, including NSCLC, with a manageable safety profile when combined with cytotoxic agents. Pembrolizumab (Keytruda®), a humanized IgG4 monoclonal antibody against programmed cell death protein 1 (PD-1), is indicated as a single agent as the first-line treatment of patients with NSCLC expressing programmed death-ligand 1 protein (PD-L1) (tumor proportion score [TPS] ≥1%) in US as determined by an approved test, and in EU if [TPS] ≥50%, and for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy in US and for the treatment of locally advanced or metastatic non-small cell lung carcinoma in adults whose tumors express PD-L1 with a ≥1% TPS and who have received at least one prior chemotherapy regimen in EU.

Pembrolizumab is also approved in combination with pemetrexed and platinum chemotherapy, as first-line treatment of patients with metastatic NSQ NSCLC, with no *EGFR* or *ALK* genomic tumor aberrations, and in combination with carboplatin and paclitaxel, as first-line treatment of patients with metastatic squamous NSCLC (1).

Combined ICI and VEGF/VEGF receptor inhibition have shown benefit in multiple tumor types through immune modulation. Pembrolizumab and ramucirumab (P+R) were evaluated in patients with advanced, ICI-exposed, in a substudy of Lung-MAP1, a master protocol for patients with Stage IV previously treated NSCLC. In this randomized, Phase II study from the Lung-MAP platform,136 patients were randomized to receive pembrolizumab + ramucirumab or the Investigator's choice of standard therapeutic regimens (SOC). Overall survival (OS) was significantly improved with P+R compared to SOC: median (95% CI) OS was 14.5 (13.9 to 16.1) months for P+R: and 11.6 (9.9 to 13.0) months for SOC (HR: 0.69 [0.51 to 0.92]. P value from the standard log-rank test equal to 0.05 and 0 .15 from the weighted log-rank test. Neither progression-free survival (PFS) or objective response rate (ORR) differed between the treatment arms (2).

Based on the experience of the first patients treated in ACT16146 for the dosage of tusamitamab ravtansine and pembrolizumab and the experience of the doublet cohort, the starting dose for tusamitamab ravtansine will be 150 mg/m^2, ramucirumab 10 mg/kg and pembrolizumab 200 mg, every 3 weeks.

Preliminary safety data for the tusamitamab ravtansine and pembrolizumab combination from Study ACT16146 as of 17 June 2022 indicate the combination was well tolerated.

The aim of this study is to evaluate the safety, tolerability and antitumor activity (efficacy) of tusamitamab ravtansine in combination with ramucirumab alone, and tusamitamab ravtansine combined with both ramucirumab and pembrolizumab in participants with CEACAM5-positive (CEACAM5 ≥50%) NSQ NSCLC tumors.

Objectives and endpoints

Doublet cohort

Objectives	Endpoints
Primary	
• **Part 1 (safety run-in):** To assess the tolerability and to confirm the recommended dose of tusamitamab ravtansine in combination with ramucirumab in the NSQ NSCLC population.	• **Part 1** Incidence of study drug-related dose-limiting toxicity (DLT) at Cycle 1 and Cycle 2 (C1D1 to C2D14). Anticipated DLT includes, but is not limited to, corneal toxicity.
• **Part 2:** To assess the antitumor activity of tusamitamab ravtansine in combination with ramucirumab in the NSQ NSCLC population.	• **Part 2:** Objective response rate (ORR) defined as proportion of participants with confirmed complete response (CR) or partial response (PR) as best overall response (BOR) determined per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.
Secondary	
• To assess the safety and tolerability of tusamitamab ravtansine in combination with ramucirumab	• Incidence of treatment emergent adverse events (TEAEs) and serious adverse events (SAEs) and laboratory abnormalities according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) V5.0
• To assess the durability of the response to treatment with tusamitamab ravtansine in combination with ramucirumab	• Duration of response (DOR), defined as the time from first documented evidence of CR or PR until progressive disease (PD) determined per RECIST v1.1 or death from any cause, whichever occurs first
• To assess anti-tumor activity of tusamitamab ravtansine in combination with ramucirumab on progression free survival (PFS) and disease control rate (DCR)	• Progression-free survival, defined as the time from the first investigational medicinal product (IMP) administration to the date of the first documented disease progression or death due to any cause, whichever comes first • Disease control rate (DCR), defined as the percentage of participants who have achieved confirmed CR, confirmed PR or stable disease as per RECIST v1.1
• To assess the pharmacokinetic (PK) profiles of tusamitamab ravtansine (SAR408701) and ramucirumab when given in combination	• Pharmacokinetic parameters of tusamitamab ravtansine (SAR408701) and ramucirumab
• To assess the immunogenicity of tusamitamab ravtansine (SAR408701) when given in combination with ramucirumab	• Incidence of anti-therapeutic antibodies (ATAs) against tusamitamab ravtansine (SAR408701)

Abbreviations: ATA=antitherapeutic antibody; BOR=best overall response; CEA=carcinoembryonic antigen; CR=complete response; DLT=dose-limiting toxicity; DCR=disease control rate; DOR=duration of response; IMP=investigational medicinal product; NCI CTCAE= National Cancer Institute Common Terminology Criteria for Adverse Events; NSQ NSCLC=non-squamous, non-small-cell lung cancer; PD=progressive disease; PFS=progression-free survival; PK=pharmacokinetic; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors.

Triplet cohort

Objectives	Endpoints
Primary	
• To assess the tolerability and to confirm the recommended dose of tusamitamab ravtansine in combination with ramucirumab and pembrolizumab in the NSQ NSCLC population.	• Incidence of study drug-related dose-limiting toxicity (DLT) at Cycle 1 (C1D1 to C1D21). Anticipated DLT includes, but is not limited to, corneal toxicity.
Secondary	
• To assess the safety and tolerability of tusamitamab ravtansine in combination with ramucirumab and pembrolizumab	• Incidence of treatment emergent adverse events (TEAEs) and serious adverse events (SAEs) and laboratory abnormalities according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) V5.0
• To assess the antitumor activity of tusamitamab ravtansine in combination with ramucirumab and pembrolizumab in the NSQ NSCLC population.	• Objective response rate (ORR) defined as proportion of participants with confirmed complete response (CR) or partial response (PR) as best overall response (BOR) determined per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.
• To assess the immunogenicity of tusamitamab ravtansine when given in combination with ramucirumab and pembrolizumab	• Incidence of anti-therapeutic antibodies (ATAs) against tusamitamab ravtansine

Abbreviations: ATA=antitherapeutic antibody; BOR=best overall response; CR=complete response; DLT=dose-limiting toxicity; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; NSQ NSCLC=non-squamous, non small-cell lung cancer; PK=pharmacokinetic; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors.

Overall design:

This is a Phase 2, open-label, single-arm, 2 cohorts, multi-center study assessing safety, efficacy (antitumor activity), and PK of the combination of tusamitamab ravtansine and ramucirumab (Doublet cohort), and tusamitamab ravtansine, ramucirumab, and pembrolizumab (Triplet cohort) in patients with metastatic, CEACAM5-positive (defined as CEACAM5 immunohistochemical [IHC] intensity ≥2+ in ≥50% of cells) NSQ NSCLC tumors, previously treated with platinum-based chemotherapy and an ICI. The prescreening phase will correspond to the period for collection of a participant's tumor sample to allow determination of CEACAM5 status by central IHC. Only participants with NSQ NSCLC determined to be CEACAM5-positive by central IHC will go through protocol screening procedures during the screening phase.

The doublet cohort will be in 2 parts:

Part 1 (Safety Run-In): In Part 1, participants will receive ramucirumab 8 mg/kg followed by tusamitamab ravtansine every 2 weeks to assess the tolerability of the combination to be used in the subsequent part of the study. The first 3 participants will receive ramucirumab at 8 mg/kg followed by tusamitamab ravtansine 100 mg/m^2 every 2 weeks. Administration of tusamitamab ravtansine will be initiated at least 1 hour after the completion of ramucirumab infusion.

As no overlap in the safety profiles for ramucirumab and tusamitamab ravtansine is anticipated, the starting dose for tusamitamab ravtansine is selected as the maximum tolerated dose (MTD) used in studies evaluating tusamitamab ravtansine as monotherapy.

A minimum delay of 1 week is required between the initial dose in the first participant treated in a DL cohort and dosing the next 2 participants treated at the same DL.

- If ≤1/3 participants treated at the starting dose experiences a DLT, 3 additional participants will be treated to confirm the tolerability of the combination.
  - If ≤1/6 participants treated at the starting dose experiences a DLT, the starting dose will be the RP2D.
  - If ≥2/6 participants treated at the starting dose experience DLTs, the dose will be de-escalated to DL -1.
- If ≥2/3 participants treated at the starting dose experience DLTs, the dose will be de-escalated to DL minus 1 (DL -1).
- If ≤1 of the first 3 participants treated at DL -1 experiences a DLT, 3 additional participants will be treated at this DL.
  - If ≤1/6 participants treated at DL -1 experiences a DLT, DL-1 will be the RP2D.
  - If ≥2/6 participants treated at DL -1 experience a DLT, an alternative dosage might be considered or the doublet cohort may be stopped.
- If ≥2/3 participants treated at DL -1 experience a DLT, an alternative dosage might be considered or the doublet cohort may be stopped.

Note: If ≥2/6 or ≥2/3 participants treated at DL -1 experience DLTs, an alternative dosage might be considered from a safety viewpoint by the Sponsor after consulting the Study Committee (SC).

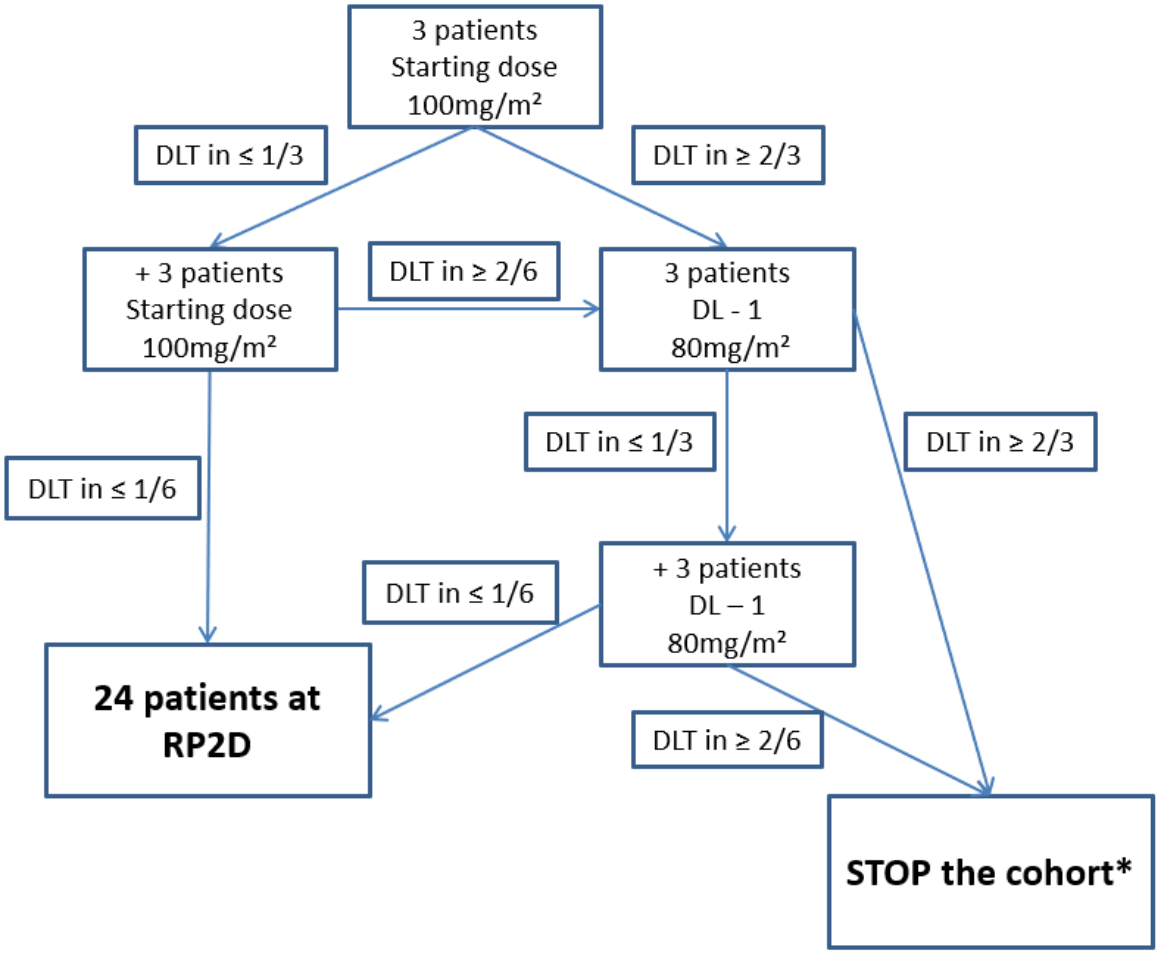
Table 1 shows dose reduction in the case of DLTs occurring in 2 or more of the first 3 participants or of 6 participants in a DL cohort in Part 1. Figure 1 shows the decision tree for doses to be administered in Part 1.

Table 1 - Dose reduction for the doublet cohort Part 1 (safety run-in)

Dose level (DL)	Tusamitamab ravtansine	Ramucirumab
Starting dose	100 mg/m^2 Q2W	8 mg/kg Q2W
Minus -1 (DL-1)	80 mg/m^2 Q2W	8 mg/kg Q2W

BSA=body surface area; DL=dose level; Q2W=every 2 weeks.
Infusion of tusamitamab ravtansine will be administered at least 1 hour after the end of ramucirumab infusion. For patients with a BSA >2.20 m^2, the SAR408701 dose will be calculated based on a BSA of 2.20 m^2.

Figure 1 - Decision tree for the doublet cohort Part 1 for tusamitamab ravtansine



* Note: In case of 2 or more DLTs at DL -1, the cohort may be stopped or the dosage reconsidered.
Abbreviations: DL -1=dose level -1 (80 mg/m²); DLT=dose-limiting toxicity; RP2D=recommended dose.

Part 2: 30 treated participants evaluable for response are planned (the 6 participants from the safety run-in treated at the RP2D will be included).

<u>The triplet cohort will have only 1 part</u>:

Participants will receive ramucirumab 10 mg/kg, tusamitamab ravtansine followed by pembrolizumab 200 mg, every 3 weeks to assess the tolerability of the combination to be used in future clinical studies. The first 3 participants will receive ramucirumab at 10 mg/kg, tusamitamab ravtansine 150 mg/m^2 followed by pembrolizumab 200 mg every 3 weeks. Administration of tusamitamab ravtansine will be initiated at least 1 hour after the completion of ramucirumab infusion.
The starting dose for tusamitamab ravtansine is 150 mg/m^2 and was defined based on findings from first-in-human study TED13751. In this study, the RP2D for tusamitamab ravtansine given Q3W was 170 mg/m^2. Given that tusamitamab ravtansine exposure PK parameters at Cycle 1 of administration as a single agent of 170 mg/m^2 Q2W were significantly associated with the

occurrence of Grade ≥2 corneal events, it is anticipated that 150 mg/m^2 may result in less ocular toxicity, and overall will be better tolerated than 170 mg/m^2. In addition, this dose corresponds to the same dose intensity as with the recommended 100 mg/m² Q2W dose.

A minimum delay of 1 week is required between the initial dose in the first participant treated in a DL cohort and dosing the next 2 participants treated at the same DL.

- If ≤1/3 participants treated at the starting dose experiences a DLT, 3 additional participants will be treated to confirm the tolerability of the combination.
  - If ≤1/6 participants treated at the starting dose experiences a DLT, the starting dose will be the RP2D.
  - If ≥2/6 participants treated at the starting dose experience DLTs, the dose will be de-escalated to DL -1.
- If ≥2/3 participants treated at the starting dose experience DLTs, the dose will be de-escalated to DL minus 1 (DL -1).
- If ≤1 of the first 3 participants treated at DL -1 experiences a DLT, 3 additional participants will be treated at this DL.
  - If ≤1/6 participants treated at DL -1 experiences a DLT, DL-1 will be the RP2D.
  - If ≥2/6 participants treated at DL -1 experience a DLT, an alternative dosage might be considered or the triplet cohort may be stopped.
- If ≥2/3 participants treated at DL -1 experience a DLT, an alternative dosage might be considered or the triplet cohort may be stopped.

Note: If ≥2/6 or ≥2/3 participants treated at DL -1 experience DLTs, an alternative dosage might be considered from a safety viewpoint by the Sponsor after consulting the Study Committee (SC).

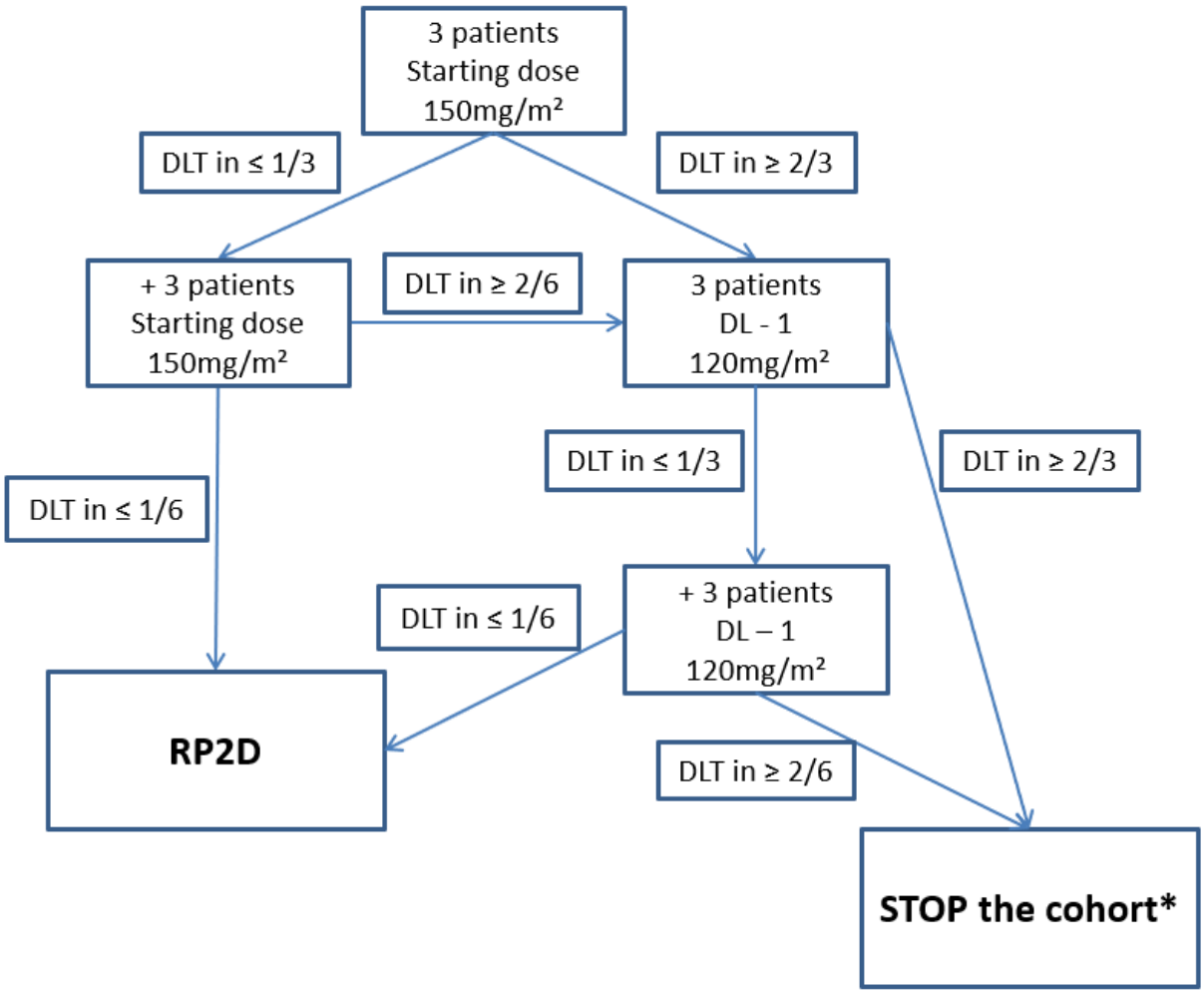
Table 2 shows dose reduction in the case of DLTs occurring in 2 or more of the first 3 participants or of 6 participants in a DL triplet cohort. Figure 2 shows the decision tree for doses to be administered.

Table 2 - Dose reduction for the triplet cohort

Dose level (DL)	Tusamitamab ravtansine	ramucirumab	pembrolizumab
Starting dose	150 mg/m^2 Q3W	10 mg/kg Q3W	200 mg Q3W
Minus -1 (DL-1)	120 mg/m^2 Q3W	10 mg/kg Q3W	200 mg Q3W

DL=dose level; Q3W=every 3 weeks.
Infusion of tusamitamab ravtansine will be administered at least 1 hour after the end of ramucirumab infusion. For patients with a BSA >2.20 m^2, the tusamitamab ravtansine dose will be calculated based on a BSA of 2.20 m^2.

Figure 2 - Decision tree for triplet cohort for tusamitamab ravtansine



* Note: In case of 2 or more DLTs at DL - 1, the cohort may be stopped or the dosage reconsidered.
Abbreviations: DL -1=dose level -1 (120 mg/m^2); DLT=dose-limiting toxicity; RP2D=recommended dose.

The study cut-off for the secondary ORR endpoint analysis of triplet cohort corresponds to the date on which all evaluable treated patients have had at least 2 post baseline tumor assessments, experienced confirmed objective response, or have discontinued the study for any reason. This study cut-off will occur approximately 4.5 months after the date of the first IMP administration of the last participant: 3 months for 2 tumor assessments and 1.5 months if a confirmation of response is needed.

Disclosure Statement: This is a single-arm, 2 cohorts, open-label, treatment study with no masking in patients with previously treated metastatic NSQ NSCLC.

Number of participants:

In the doublet cohort, approximately 225 participants will be prescreened to achieve up to approximately 36 treated participants, based on an estimated CEACAM5 prescreening failure rate of 80% and an estimated study screen-failure rate of 20%.

In the triplet cohort, approximately 74 participants will be prescreened to achieve up to approximately 12 DLT evaluable participants, based on the doublet cohort CEACAM5 prescreening failure rate of 79% and an estimated study screen-failure rate of 23%.

Intervention groups and duration:

The duration of the study for a participant will include:

- **Screening period:** up to 28 days.
- **Treatment period:** once successfully screened, enrolled participants may receive study intervention until disease progression, unacceptable AE, or the participant's or investigator's decision to stop the treatment. Each cycle of treatment will have a duration of 2 weeks in the doublet cohort and 3 weeks in triplet cohort. After discontinuing study intervention, participants will return to the study site approximately 30 days after the last investigational medicinal product (IMP) administration or before the participant receives another anti-cancer therapy, whichever is earlier, for end-of-treatment assessments.
- **Safety follow-up visit**: will be performed approximately 90 days after the last dose of IMP. If any ongoing related AE/SAE is resolved or stabilized, no further follow-up visit is needed.

The expected duration of study intervention for participants may vary, based on progression date; median expected duration of study per participant is estimated as 11 months (up to 1 month for screening, a median of 6 months for treatment, and a median of 4 months for end-of-treatment assessments and safety follow-up visit).

Study interventions

Study interventions include tusamitamab ravtansine, ramucirumab, and pembrolizumab. To prevent hypersensitivity reactions, each administration will be preceded by premedication. Each cycle of treatment will have a duration of 2 weeks in the doublet cohort, and 3 weeks in the triplet cohort.

Investigational medicinal products

Ramucirumab

Ramucirumab will be administered prior to administration of tusamitamab ravtansine.

- Formulation: CYRAMZA® (ramucirumab) is a concentrate for solution for infusion supplied in 10 mL or 50 mL single-use vial. Each vial contains either 100 mg ramucirumab in 10 mL (10 mg/mL) or 500 mg ramucirumab in 50 mL (10 mg/mL).
- Route of administration: intravenous (IV) infusion.
- Dose regimen:
  - In the doublet cohort, ramucirumab will be administered as an 8 mg/kg IV infusion over 1 hour on Day 1 of every 2-week cycle. Each administration will be preceded by premedication (as per the approved product label) to prevent hypersensitivity reaction.

- In the triplet cohort, ramucirumab will be administered as a 10 mg/kg IV infusion over 1 hour on Day 1 of every 3-week cycle. Each administration will be preceded by premedication (as per the approved product label) to prevent hypersensitivity reaction.

Tusamitamab ravtansine

tusamitamab ravtansine infusion will start ≥1 hour after the end of ramucirumab infusion.

- Formulation:
  Tusamitamab ravtansine is supplied as a 25 mL extractable volume of concentrate for solution for infusion of 125 mg contained in a 30 mL type I glass vial.
- Route of administration: IV infusion.
- Dose regimen:
  - In the doublet cohort, tusamitamab ravtansine 100 mg/m^2 (or 80 mg/m^2, if deemed the appropriate dose by the SC) will be administered via IV infusion over 1 hour, 30 minutes on Day 1, and then every 2 weeks.
  - In the triplet cohort, tusamitamab ravtansine 150 mg/m^2 (or 120 mg/m^2, if deemed the appropriate dose by the SC) will be administered via IV infusion over 1 hour, 30 minutes on Day 1, and then every 3 weeks.
- For patients with a body surface area (BSA) >2.20 m^2, the dose of tusamitamab ravtansine will be calculated based on a BSA of 2.20 m^2.

Pembrolizumab

In the triplet cohort, pembrolizumab will be administered after ramucirumab and tusamitamab ravtansine.

- Formulation: Keytruda® (pembrolizumab) is a concentrate for solution for infusion supplied in 100 mg/4 mL (25 mg/mL) solution in single-dose vials.
- Route of administration: intravenous (IV) infusion.
- Dose regimen: pembrolizumab will be administered as a 200 mg IV infusion over 30 minutes on Day 1 and then Q3W.

Noninvestigational medicinal products:

Premedication:

Both tusamitamab ravtansine and ramucirumab have potential risk of infusion-related allergic reaction; therefore, premedication with an IV histamine H1 antagonist (diphenhydramine 50 mg IV or equivalent; eg, cetirizine, promethazine, dexchlorpheniramine, according to local approval and availability) given approximately at least 15 minutes before ramucirumab administration is required for all participants. If a participant previously experienced an infusion-related reaction (IRR) following a dose of ramucirumab or tusamitamab ravtansine, premedication for subsequent infusions will also include dexamethasone 10 mg IV and acetominophen (paracetamol). All drugs used as premedication will be entered on the concomitant premedication page.

Statistical considerations:

- **Sample size calculations:**

  This study is divided into 2 cohorts:

  Doublet cohort: the cohort is divided in 2 parts: a safety run-in (Part 1) and Part 2. In the safety run-in Part, 6 to 12 DLT-evaluable participants will be enrolled in order to confirm the RP2D. In Part 2, the plan is to enroll and treat enough participants to attain a total of 30 participants evaluable for activity (ie, having at least 1 post-baseline tumor assessment). The 6 participants treated at the RP2D will also be evaluable for Part 2.

  Triplet cohort: the cohort will have only 1 part: a safety run-in. 6 to 12 DLT-evaluable participants will be enrolled in order to confirm the RP2D.

- **Main analysis populations:**
  - **All-treated population:** All registered participants exposed to the study treatment, regardless of the amount of treatment administered. This population is the primary population for analysis of all efficacy parameters.
  - **DLT-Evaluable population:** For the doublet cohort: All participants who received 2 cycles with at least 80% of the intended dose for both tusamitamab ravtansine and ramucirumab at each of the 2 first infusions unless they discontinued the study intervention before the end of Cycle 2 due to a DLT. For the triplet cohort: Participants who received 1 cycle with at least 80% of the intended dose for each IMP of the combination. Participants should have completed Cycle 1 unless they experienced a DLT before the end of Cycle 1.
  - **Activity population (applicable for doublet cohort only):** All treated participants who have measurable disease at study entry and at least 1 postbaseline evaluable tumor assessment. Participants with early clinical progression or early death due to disease progression (ie, before first planned tumor assessment) will also be included in this set. This population is the secondary population for analysis of efficacy parameters of the doublet cohort.
  - **PK population:** All participants from the All-Treated population who actually received at least 1 dose or a part of a dose of tusamitamab ravtansine or ramucirumab with at least 1 evaluable postbaseline concentration.
  - **ATA population:** All treated participants with at least 1 post-baseline ATA result (negative, positive, or inconclusive).
- **Analysis of Primary endpoints for the doublet cohort:**
  - Objective response rate (ORR) will be summarized using descriptive statistics and 95% exact confidence intervals (CIs) will be provided using the Clopper-Pearson method.
  - The DLTs observed during the DLT observation period (Cycle 1 and Cycle 2), will be summarized on the DLT-evaluable population, by dose level. In addition, AEs that

meet the DLT criteria in subsequent cycles will be summarized on the all-treated population. Details will be provided by participant.

- **Analysis of Primary endpoint for the triplet cohort:**
  - The DLTs observed during the DLT observation period (Cycle 1), will be summarized on the DLT-evaluable population, by dose level. In addition, AEs that meet the DLT criteria in subsequent cycles will be summarized on the all-treated population. Details will be provided by participant.
- **Analysis of secondary efficacy endpoints for the doublet cohort:**
  - Duration of response will be summarized for the subgroup of participants who achieve confirmed objective response in the all-treated population with descriptive statistics using Kaplan-Meier methods. The median DOR and associated 95% CI will be provided.
  - Progression-free survival will be summarized using Kaplan-Meier methods. The median PFS times and associated 95% CI will be provided, along with probabilities of being progression-free at different time points.
  - Disease control rate (DCR) will be summarized using descriptive statistics and 95% exact confidence intervals (CIs) will be provided using the Clopper-Pearson method.
- **Analysis of secondary efficacy endpoints for the triplet cohort:**
  - ORR will be summarized using descriptive statistics and 95% exact confidence intervals (CIs) will be provided using the Clopper-Pearson method.
- **Analysis of safety endpoints:**
  - Number and percentage of participants experiencing TEAEs by primary system organ class (SOC) and preferred term (PT) will be summarized by NCI-CTCAE V5.0 Grade (all grades, and Grade ≥3) for the all-treated population. Similar summaries will be prepared for treatment-related TEAEs, TEAEs leading to definitive discontinuation, TEAEs leading to dose modification, serious TEAEs, TEAEs with fatal outcome, adverse events of special interest (AESIs), and AEs/SAEs occurring during the post-treatment period. In addition, the number (%) of participants with any Grade 5 AE (TEAE and post-treatment) will be summarized.
  - Hematology and clinical chemistry results will be graded according to the NCI-CTCAE V5.0, when applicable. Number and percentage of participants with laboratory abnormalities (all grades and by grade) using the worst grade during the treatment period will be provided for the all-treated population.

Data Monitoring Committee: No

1.2 SCHEMA

A graphical representation of study design is shown in Figure 3:

Figure 3 - 3a-3b-3c - Graphical description of study design

Doublet cohort:

Figure 3a:

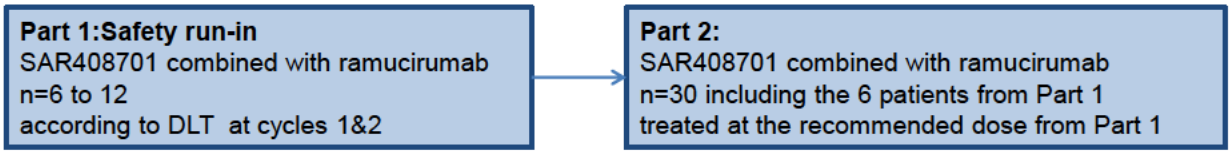
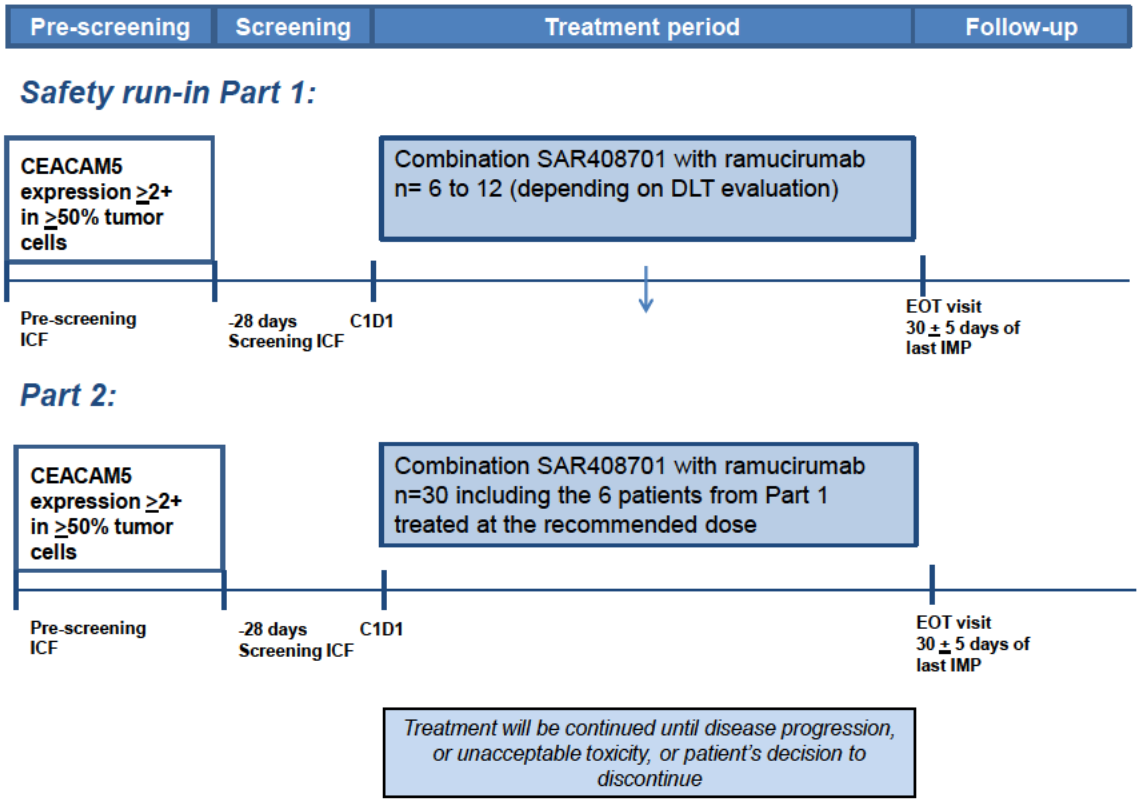
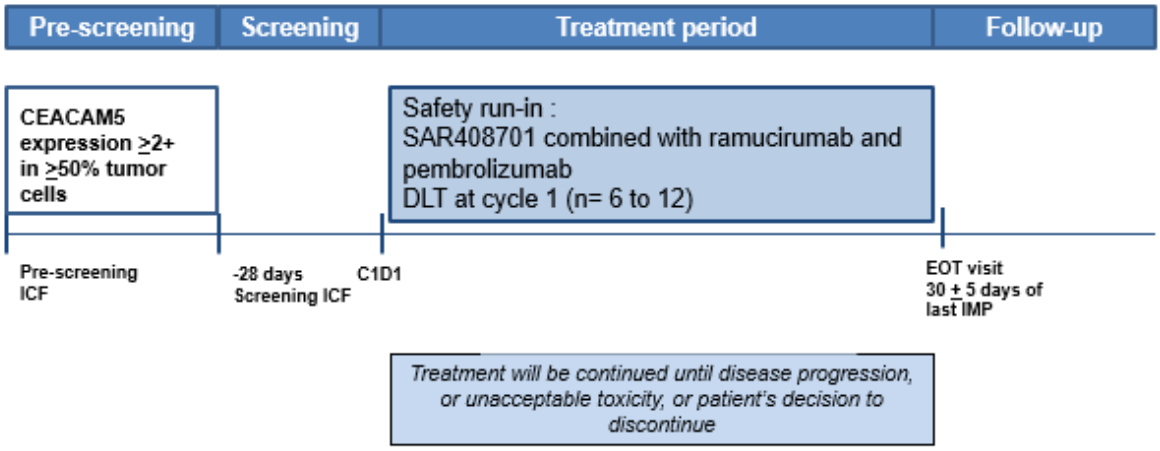


Figure 3b:



Triplet cohort:

Figure 3c:



1.3 SCHEDULE OF ACTIVITIES (SOA)

1.3.1 Study flow chart - Doublet cohort

Procedure	Pre-screening[a]	Screening[b]	Treatment cycle 1		Treatment cycle 2 +		End of treatment	90 (±7) Days (3 month) Follow-up[d]	Notes*
Day		Days to first infusion	D1		14 (±2) days from previous infusion		30 (±5) days from last infusion		
			Pre-infusion[c]	EOI	Pre-infusion[c]	Every 8 weeks (±7 days)			
CEACAM5 expression status[a] (archival or fresh tumor tissue) – central IHC/ prescreening Informed consent	X								
Informed Consent		X							
Inclusion/exclusion criteria		≤28	X						Section 5.1, 5.2
Demography, medical/surgical/disease/smoking history[e]		≤28							
NSCLC characteristics[f]	X	≤28							
Height		≤7							
Performance status (ECOG)		≤7	X		X		X	X	Section 8.2.1, 8.2.3
Physical examination,including vital signs, body weight[g]		≤7	X		X		X	X	Section 8.2.1
Hematology[h]		≤7	X		X		X		Section 8.2.5, 10.2 (Appendix 2)
Coagulation[i]		≤7	X		X		X		Section 10.2 , (Appendix 2)
Clinical blood chemistry[j]		≤7	X		X		X		Section 8.2.5, 10.2 (Appendix 2)
Urinalysis[k]		≤7	X		X				Section 10.2 , (Appendix 2)
HBsAg & HCV serology and HIV test (only if required at country level)		X							Section 10.8 , (Appendix 8)

Procedure	Pre-screening[a]	Screening[b]	Treatment cycle 1		Treatment cycle 2 +		End of treatment	90 (±7) Days (3 month) Follow-up[d]	Notes*
Day		**Days to first infusion**	**D1**		**14 (±2) days from previous infusion**		**30 (±5) days from last infusion**		
			Pre-infusion[c]	**EOI**	**Pre-infusion[c]**	**Every 8 weeks (±7 days)**			
Urine or Serum pregnancy test[l]		≤7			X		X	X	Section 10.2 (Appendix 2) Section 10.5 (Appendix 5)
Left ventricular ejection fraction (MUGA/echocardiogram)[m]		≤28							Section 8.2.4.2
12-lead ECG[n]		≤7	X	X	X		X		Section 8.2.4.1
Specific ocular tests[o]		≤28					X		Section 8.2.2
Tusamitamab ravtansine/Ramucirumab administration			X		X				Section 6.1
AE assessment[p]	X	Continuously throughout the study period							Section 8.2, 8.3, 10.3 (Appendix 3)
Concomitant medication[q]		X	Continuously throughout the study period						Section 6.5
Tumor assessment – RECIST v1.1 - CT/MRI; relevant surrogate markers[r]		≤28				X	X	X	Section 8.1
Circulating CEA[s]	X	≤28				X	X	X	
IgG			X						
Record further anticancer therapy								X	
Tusamitamab ravtansine and ramucirumab PK			Refer to PK/ATA flowchart, Section 1.3.3						Section 8.5
Tusamitamab ravtansine Immunogenicity			Refer to PK/ATA flowchart, Section 1.3.3						Section 8.9

Abbreviations: AE=adverse event; AESI=AE of special interest; ALT (SGPT)=alanine aminotransferase; AST (SGOT)=aspartate aminotransferase; ATA=antitherapeutic antibody; CEA=carcinoembryonic antigen; CEACAM5=carcinoembryonic antigen-related cell adhesion molecule 5; CR=complete remission; CT=computed tomography; eCRF=electronic case report form; ECOG=Eastern Cooperative Oncology Group (performance status); ECG=electrocardiogram; EOI=end of infusion; HBsAg=hepatitis B virus surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus; IMP=investigational medicinal product; LVEF=left ventricular ejection fraction; MRI=magnetic resonance imaging; MUGA=multigated acquisition scan; NSCLC=non-small-cell lung cancer; PD=progressive disease; PK=pharmacokinetic; PR=partial response; RBC=red blood cells; RECIST=Response Evaluation Criteria in Solid Tumors; SAE=serious AE; SD=stable disease; WBC=white blood cells.

a Prescreening: a prescreening Informed Consent will be signed by the patient for CEACAM5 assay on archival or fresh tumor tissue and circulating CEA assay unless results are available from an assay for circulating CEA and from CEACAM5 testing for another study; in this case, an addendum to the informed consent will be sufficient.

b Screening: Informed consent should be signed before any study specific procedures. It can be signed more than 28 days prior to initiation of therapy. Screening time indicates in which timeframe exams used to support eligibility have to be done prior to initiation of therapy. 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: participants must have confirmed CEACAM5 expression as assessed centrally. Baseline evaluation should be completed within 1 week prior to initiation of therapy, except for tumor assessment, circulating CEA, echocardiography, and ocular tests that may be performed within 4 weeks prior to the first IMP administration. Results of these tests should be reviewed by the Investigator prior to initiation of therapy.

c D1 pre-dose: Cycle 1 D1 refers to the day the participant receives the initial dose of IMP. D1 of Cycle 2 and of each subsequent cycle corresponds to D15 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, coagulation and urinalysis 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 visit: 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 (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 visit. Participants who stopped treatment before documented progressive disease (PD; ie, achieving stable disease [SD], or complete or partial response [CR or PR]) should undergo a tumor assessment and an on-site follow-up visit every 12 weeks (±7 days) after the last tumor assessment until radiological disease progression, death, study cut-off date of the secondary ORR endpoint of the triplet cohort, initiation of further anti-cancer therapy, or withdrawal of participant's consent, whichever comes first. Participants with documented disease progression should attend an on-site follow-up visit 90 days after the last dose of study medication. If every ongoing related AE/SAE/AESI is resolved or stabilized, no further follow-up visit is needed.

e Disease history includes previous antitumor therapy (type, start and end dates, reason for discontinuation and response to the therapy) and smoking history.

f NSCLC characteristics will include histologic types, stage at diagnosis, disease extent at study entry, (collected at screening) and specific mutations including PD-1 expression status (to be collected only at prescreening).

g Physical examination will include: vital signs (temperature, blood pressure, heart rate) and examination of major body systems. Signs and symptoms will be reported in the electronic case report form (eCRF) as AEs only if they are still present at the time of first IMP administration

h Hematology: Hemoglobin, hematocrit, RBC, WBC with differential, platelet counts. These tests will be done before IMP administration at each cycle. If Grade 4 neutropenia, assess absolute neutrophil count (ANC) every 2-3 days until ANC ≥0.5 x 10^9/L. During first 2 cycles, hematology will be performed weekly.

i Coagulation: International normalized ratio (INR), aPTT.

j Clinical blood chemistry: Liver function tests: SGOT (AST), SGPT (ALT), total bilirubin, conjugated bilirubin, AP. Renal function tests: Urea (or BUN) & creatinine. Electrolytes: Sodium, potassium, calcium, glucose, Others: LDH, albumin and total proteins. During first cycle, liver function tests will be performed weekly. The liver function tests and renal function tests will be done before IMP administration at each cycle, unless clinically appropriate. In case of Grade ≥3 liver function abnormal tests, additional tests will be repeated every 2-3 days until recovery to baseline value.

k Urinalysis tests on morning spot will be performed by dipstick at baseline, and at every treatment cycle. In case of proteinuria ≥ ++ (dipstick), proteinuria quantification by proteinuria/24 h should be performed.

l Serum pregnancy test: women of childbearing potential must have a negative serum pregnancy test result within 7 days prior to the initial dose of IMP. A pregnancy test (serum/urine) will be repeated every 4 weeks before IMP administration, and a serum test will be repeated at the End of Treatment evaluation (30±5 days after the last IMP administration), and at the Follow-up visit (90±7 days after last IMP dose).

m Echocardiogram or MUGA scan: left ventricular ejection fraction (LVEF) will be evaluated during screening period, and whenever clinically indicated.

n 12-lead ECG is required at baseline (In case the ECG performed less than 7 days before 1st IMP administration is considered as normal, there is no need to repeat it just before the 1st IMP) before starting the and after completing the first IMP administration (within 30 minutes after the end of tusamitamab ravtansine infusion).The ECG after the infusion at cycle1 should be performed at any case; before IMP administration at each cycle; and at the End of treatment evaluation, 22 to 30 days after last IMP administration.

o Specific ocular tests will include assessment of ocular/visual symptoms and ocular exams including visual acuity, slit lamp under dilatation, and Schirmer's test at screening and whenever clinically indicated.

p AE: 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 the prescreening period after fresh biopsy.

q 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.

r Tumor assessment will be made at every 8 weeks interval (±7 days window) during the study treatment period until radiological disease progression; initiation of further anti-cancer therapy; death; or study cut-off of the secondary ORR endpoint of the triplet cohort. The scheduled tumor assessment time point will not be modified in case of a cycle delay.

s CEA samples should be collected before IMP infusion.

1.3.2 Study flow chart - Triplet cohort

Procedure	Pre-screening[a]	Screening[b]	Treatment cycle 1		Treatment cycle 2 +		End of treatment	90 (±7) Days (3 month) Follow-up[d]	Notes*
Day		Days to first infusion	D1		21 (±3) days from previous infusion		30 (±5) days from last infusion		
			Pre-infusion[c]	EOI	Pre-infusion[c]	Every 6 weeks (±7 days)			
CEACAM5 expression status[a] (archival or fresh tumor tissue) – central IHC/ prescreening Informed consent	X								
Informed Consent		X							
Inclusion/exclusion criteria		≤28	X						Section 5.1, 5.2
Demography, medical/surgical/disease/smoking history[e]		≤28							
NSCLC characteristics[f]	X	≤28							
Height		≤7							
Performance status (ECOG)		≤7	X		X		X	X	Section 8.2.1, 8.2.3
Physical examination,including vital signs, body weight[g]		≤7	X		X		X	X	Section 8.2.1
Hematology[h]		≤7	X		X		X		Section 8.2.5, 10.2 (Appendix 2)
Coagulation[i]		≤7	X		X		X		Section 10.2 , (Appendix 2)
Clinical blood chemistry[j]		≤7	X		X		X		Section 8.2.5, 10.2 (Appendix 2)
Thyroid function		≤7			X		X		
Urinalysis[k]		≤7	X		X				Section 10.2 , (Appendix 2)
HBsAg & HCV serology and HIV test (only if required at country level)		X							Section 10.8 , (Appendix 8)

Procedure	Pre-screening[a]	Screening[b]	Treatment cycle 1		Treatment cycle 2 +		End of treatment	90 (±7) Days (3 month) Follow-up[d]	Notes*
Day		Days to first infusion	D1		21 (±3) days from previous infusion		30 (±5) days from last infusion		
			Pre-infusion[c]	EOI	Pre-infusion[c]	Every 6 weeks (±7 days)			
Urine or Serum pregnancy test[l]		≤7			X		X	X	Section 10.2 (Appendix 2) Section 10.5 (Appendix 5)
Left ventricular ejection fraction (MUGA/echocardiogram)[m]		≤28							Section 8.2.4.2
12-lead ECG[n]		≤7	X	X	X		X		Section 8.2.4.1
Specific ocular tests[o]		≤28					X		Section 8.2.2
Tusamitamab ravtansine/Ramucirumab/Pembrolizumab administration			X		X				Section 6.1
AE assessment[p]	X	Continuously throughout the study period							Section 8.2, 8.3, 10.3 (Appendix 3)
Concomitant medication[q]		X	Continuously throughout the study period						Section 6.5
Tumor assessment – RECIST v1.1 - CT/MRI; relevant surrogate markers[r]		≤28				X	X	X	Section 8.1
Circulating CEA[s]	X	≤28				X	X	X	
IgG			X						
Record further anticancer therapy								X	
Tusamitamab ravtansine PK			Refer to PK/ATA flowchart, Section 1.3.3						Section 8.5
Tusamitamab ravtansine Immunogenicity			Refer to PK/ATA flowchart, Section 1.3.3						Section 8.9

Abbreviations: AE=adverse event; AESI=AE of special interest; ALT (SGPT)=alanine aminotransferase; AST (SGOT)=aspartate aminotransferase; ATA=antitherapeutic antibody; CEA=carcinoembryonic antigen; CEACAM5=carcinoembryonic antigen-related cell adhesion molecule 5; CR=complete remission; CT=computed tomography; eCRF=electronic case report form; ECOG=Eastern Cooperative Oncology Group (performance status); ECG=electrocardiogram; EOI=end of infusion; HBsAg=hepatitis B virus surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus; IMP=investigational medicinal product; LVEF=left ventricular ejection fraction; MRI=magnetic resonance imaging; MUGA=multigated acquisition scan; NSCLC=non-small-cell lung cancer; PD=progressive disease; PK=pharmacokinetic; PR=partial response; RBC=red blood cells; RECIST=Response Evaluation Criteria in Solid Tumors; SAE=serious AE; SD=stable disease; WBC=white blood cells.

a Prescreening: a prescreening-Informed Consent will be signed by the patient for CEACAM5 assay on archival or fresh tumor tissue and circulating CEA assay unless results are available from an assay for circulating CEA and from CEACAM5 testing for another study; in this case, an addendum to the informed consent will be sufficient.

b Screening: Informed consent should be signed before any study specific procedures. It can be signed more than 28 days prior to initiation of therapy. Screening time indicates in which timeframe exams used to support eligibility have to be done prior to initiation of therapy. 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: participants must have confirmed CEACAM5 expression as assessed centrally. Baseline evaluation should be completed within 1 week prior to initiation of therapy, except for tumor assessment, circulating CEA, echocardiography, and ocular tests that may be performed within 4 weeks prior to the first IMP administration. Results of these tests should be reviewed by the Investigator prior to initiation of therapy.

c D1 pre-dose: Cycle 1 D1 refers to the day the participant receives the initial dose of IMP. D1 of Cycle 2 and of each subsequent cycle corresponds to D22 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, coagulation and urinalysis 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 visit: 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 (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 visit. Participants with documented disease progression should attend an on-site follow-up visit 90 days after the last dose of study medication. If every ongoing related AE/SAE/AESI is resolved or stabilized, no further follow-up visit is needed.

e Disease history includes previous antitumor therapy (type, start and end dates, reason for discontinuation and response to the therapy) and smoking history.

f NSCLC characteristics will include histologic types, stage at diagnosis, disease extent at study entry, (collected at screening) and specific mutations including PD-1 expression status (to be collected only at prescreening).

g Physical examination will include: vital signs (temperature, blood pressure, heart rate) and examination of major body systems. Signs and symptoms will be reported in the electronic case report form (eCRF) as AEs only if they are still present at the time of first IMP administration

h Hematology: Hemoglobin, hematocrit, RBC, WBC with differential, platelet counts. These tests will be done before IMP administration at each cycle. If Grade 4 neutropenia, assess absolute neutrophil count (ANC) every 2-3 days until ANC ≥0.5 x 10^9/L. During first cycle, hematology will be performed weekly.

i Coagulation: International normalized ratio (INR), aPTT.

j Clinical blood chemistry: Liver function tests: SGOT (AST), SGPT (ALT), total bilirubin, conjugated bilirubin, AP. Renal function tests: Urea (or BUN) & creatinine. Electrolytes: Sodium, potassium, calcium, glucose, Others: LDH, albumin and total proteins. During first cycle, liver function tests will be performed weekly. The liver function tests and renal function tests will be done before IMP administration at each cycle, unless clinically appropriate. In case of Grade ≥3 liver function abnormal tests, additional tests will be repeated every 2-3 days until recovery to baseline value.

k Urinalysis tests on morning spot will be performed by dipstick at baseline, and at every treatment cycle. In case of proteinuria ≥ ++ (dipstick), proteinuria quantification by proteinuria/24 h should be performed.

l Serum pregnancy test: women of childbearing potential must have a negative serum pregnancy test result within 7 days prior to the initial dose of IMP. A pregnancy test (serum/urine) will be repeated every 4 weeks before IMP administration, and a serum test will be repeated at the End of Treatment evaluation (30±5 days after the last IMP administration), and at the Follow-up visit (90±7 days after last IMP dose).

m Echocardiogram or MUGA scan: left ventricular ejection fraction (LVEF) will be evaluated during screening period, and whenever clinically indicated.

n 12-lead ECG is required at baseline (In case the ECG performed less than 7 days before 1st IMP administration is considered as normal, there is no need to repeat it just before the 1st IMP) before starting and after completing the first IMP administration (within 30 minutes after the end of tusamitamab ravtansine infusion); before IMP administration at each cycle; and at the End of treatment evaluation, 22 to 30 days after last IMP administration.

o Specific ocular tests will include assessment of ocular/visual symptoms and ocular exams including visual acuity, slit lamp under dilatation, and Schirmer's test at screening and whenever clinically indicated.

p AE: 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 the prescreening period after fresh biopsy.

q 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.

r Tumor assessment will be made at every 6 weeks interval (±7 days window) during the study treatment period until radiological disease progression; initiation of further anti-cancer therapy; death; or study cut-off of the secondary ORR endpoint of the triplet cohort. The scheduled tumor assessment time point will not be modified in case of a cycle delay.

s CEA samples should be collected before IMP infusion.

1.3.3 Pharmacokinetic/Anti-therapeutic Antibody Flow Charts

1.3.3.1 Doublet cohort - Part 1: Safety run-in

Intervention period		C1						C3	C4						C6 + beyond[c,d,e]	EOT
Day		D1			D4	D8	D15	D1	D1			D4	D8	D15	D1	D30 ±5 days after last IMP
Ramucirumab	IV infusion	X---	---X				X	X	X					X	X	
	Sample RNT (hours) Ref. ramucirumab SOI	SOI	EOI				336h (SOI)	SOI	SOI						SOI	
	Sample time window	(-24h, SOI)	±10 min				±48 h	(-24h, SOI)	(-24h, SOI)						(-24h, SOI)	
	PK sample ID	S00[a]	S01				S02[a,b]	S00[a]	S00[a]						S00[a,c]	
tusamitamab ravtansine	IV infusion	X---	---X				X	X	X---	---X				X	X	
	Sample RNT (hours) Ref. tusamitamab ravtansine SOI	SOI	EOI	EOI+4h	72h	168h	336h (SOI)	SOI	SOI	EOI	EOI+4h	72h	168h	336h (SOI)	SOI	
	Sample time window	(-24h, SOI)	±10 min	±30 min	±5 h	±24 h	±48 h	(-24h, SOI)	(-24h, SOI)	±10 min	±30 min	±5 h	±24 h	±48 h	(-24h, SOI)	
	PK sample ID	P00[a]	P01	P02	P03	P04	P05[a,b]	P00[a]	P00[a]	P01	P02	P03	P04	P05[a,b]	P00[a,d]	
	ATA sample ID	AB00[a]					AB01[a,b]	AB00[a]							AB00[a,e]	ABF00

Abbreviations: AESI = adverse event of special interest; ATA = Anti-therapeutic Antibody; C = Cycle; D = Day; EOI = End of infusion; EOT = End-of-treatment; IMP = Investigational Medicinal Product; IV = intravenous; P = Plasma; PK = Pharmacokinetics; RNT = Relative nominal time; S = Serum; SOI = start of infusion.

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

b Sample must be collected even if the infusion planned is not done or delayed on C2D1 (corresponding to C1D15) and on C5D1 (corresponding to C4D15).

c Ramucirumab PK samples will be collected at SOI at Cycle 7 only.

d Tusamitamab ravtansine PK samples will be collected at SOI each cycle at Cycle 6 and Cycle 7 and thereafter at Cycle 13 only.

e Tusamitamab ravtansine ATA samples will be collected at SOI at Cycle 7 and thereafter every 6 cycles (ie, C7, C13, C19...).

Note: Upon notification from the Sponsor, the sampling time-points for PK and ATA may be reduced during the course of the study, based on new information.

1.3.3.2 Doublet cohort - Part 2

Cycle		C1			C2	C3	C4		C5 + beyond [b,c,d]	EOT
Day		D1		D4	D1	D1	D1		D1	D30 ± 5 days after last IMP
Ramucirumab	IV infusion	X---	---X		X	X	X		X	
	Sample RNT (hours) Ref. ramucirumab SOI	SOI	EOI		SOI	SOI	SOI		SOI	
	Sample time window	(-24h, SOI)	±10 min		(-24h, SOI)	(-24h, SOI)	(-24h, SOI)		(-24h, SOI)	
	PK sample ID	S00[a]	S01		S00[a]	S00[a]	S00[a]		S00[a,b]	
tusamitamab ravtansine	IV infusion	X---	---X		X	X	X		X	
	Sample RNT (hours) Ref. tusamitamab ravtansine SOI	SOI	EOI	72h	SOI	SOI	SOI	EOI+1h	SOI	
	Sample time window	(-24h, SOI)	±10 min	±24 h	(-24h, SOI)	(-24h, SOI)	(-24h, SOI)	±10 min	(-24h, SOI)	
	PK sample ID	P00[a]	P01	P02	P00[a]	P00[a]	P00[a]	P01	P00[a,c]	
	ATA sample ID	AB00[a]			AB00[a]	AB00[a]			AB00[a,d]	ABF00

Abbreviations: ATA = Anti-therapeutic Antibody; C = Cycle; D = Day; EOI = End of infusion; EOT = End-of-treatment; IMP = Investigational Medicinal Product; IV = intravenous; P = Plasma; PK = Pharmacokinetics; RNT = Relative nominal time; S = Serum; SOI = start of infusion.

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

b Ramucirumab PK samples will be collected at SOI at Cycle 7 only.

c tusamitamab ravtansine PK samples will be collected at SOI each cycle at Cycles 5, 6 and 7 and thereafter at Cycle 13 only.

d tusamitamab ravtansine ATA samples will be collected at SOI at Cycle 7 and thereafter every 6 cycles (ie, C7, C13, C19...).

Note: The sampling time-points for PK and ATA may be reduced during the course of the study based on the updated knowledge of drug behavior, upon notification from the Sponsor.

1.3.3.3 Triplet cohort

Cycle		C1	C2	C3	C4	C6	C8	C13	C18 then every 5 cycles (C23, ...)	EOT
Day		D1	D1	D1	D1	D1	D1	D1	D1	D30 ±5 days after last IMP
Tusamitamab ravtansine	IV infusion	X	X	X	X	X	X	X	X	
	Sample RNT (hours) Ref. tusamitamab ravtansine SOI	SOI	SOI	SOI	SOI	SOI	SOI	SOI	SOI	
	Sample time window	(-24 h, SOI)	(-24 h, SOI)	(-24 h, SOI)	(-24 h, SOI)	(-24 h, SOI)	(-24 h, SOI)	(-24 h, SOI)	(-24 h, SOI)	
	PK sample ID	P00[a]	P00[a]	P00[a]	P00[a]	P00[a]	P00[a]	P00[a]		
	ATA sample ID	AB00[a]	AB00[a]	AB00[a]	AB00[a]	AB00[a]	AB00[a]	AB00[a]	AB00[a]	ABF00

Note: The sampling time-points for PK and ATA may be reduced during the course of the study based on the updated knowledge of drug behavior, upon notification from the Sponsor.

a Samples collected strictly before start of infusion (SOI).

ATA: anti-therapeutic antibody; C: Cycle; D: Day; EOT: end of treatment; h: hour; IMP: investigational medicinal product; IV: intravenous; P: plasma; PK: pharmacokinetics; RNT: relative nominal time; SOI: start of infusion.

2 INTRODUCTION

Despite recent progress in the treatment of advanced NSCLC, there remains a need for effective new treatment at the time of disease progression. Current therapeutic approaches combining an inhibitor of angiogenesis in combination with a systemic cytotoxic agent such as docetaxel entail serious hematological and other toxicities; therefore, targeted cytotoxic therapies may offer an improvement in safety and tolerability as well as efficacy.

One feature that can be used to target some tumor cells is surface expression of carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5), first described in 1965 as a tumor-associated antigen in human colon cancer tissue extracts (3). High levels of CEACAM5 expression have since been observed in several epithelial tumors, whereas in normal adult tissue, its expression is limited to few tissues (4, 5). Immunostaining of CEACAM5 in a large panel of human tumor tissue microarray samples has shown the highest prevalence of cell surface CEACAM5 expression in adenocarcinomas of the colon and of the stomach and its subtypes as well as NSQ NSCLC.

Maytansinoids are antimitotic agents that inhibit microtubule formation to act as very potent cytotoxic agents against tumor cell lines in vitro, with IC_{50} values 100- to 1000-fold more potent than conventional tubulin binding compounds, including docetaxel. Tusamitamab ravtansine is an antibody to CEACAM5 conjugated to the cytotoxic maytansinoid agent, (DM4). Encouraging preliminary antitumor activity of tusamitamab ravtansine in patients heavily pretreated for NSQ NSCLC has been demonstrated in an ongoing study (TED13751).

2.1 STUDY RATIONALE

Tusamitamab ravtansine is an antibody-drug conjugate (ADC) combining hu769_4D4 (SAR408377), a humanized antibody that recognizes selectively the A3-B3 extracellular domain of CEACAM5 with the potent cytotoxic maytansinoid derivative, DM4, an inhibitor of 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 NSQ NSCLC.

In the first-in-human monotherapy study (TED13751), the maximum tolerated dosage of tusamitamab ravtansine was identified to be 100 mg/m^2 every 2 weeks. Dose-limiting toxicities were mainly Grade 3 microcystic keratopathy; all were reversible. This dose is also the selected started dose for combination studies.

In the expansion phase of study TED13751, a cohort of patients with heavily pretreated NSQ NSCLC tumors testing positive for CEACAM5 (≥2+ in intensity on membranes of ≥50% of the tumor cells) have been treated with tusamitamab ravtansine at 100 mg/m^2 every 2 weeks. Results from the 64 evaluable patients showed encouraging antitumor activity associated with a response rate of 20.3% (95% CI, 12.3% to 31.7%) (6).

Ramucirumab (Cyramza®); a human IgG1 monoclonal antibody that inhibits VEGFR-2 is approved in combination with docetaxel for the treatment of patients with metastatic NSCLC.

This approval was based on the results of a Phase 3 study (REVEL) a randomized placebo-controlled trial of 1,253 patients with metastatic NSCLC previously treated with a platinum-based combination therapy. Patients were randomized to receive either ramucirumab in combination with docetaxel or placebo in combination with docetaxel. The primary endpoint was overall survival (OS). Patients who received ramucirumab in combination with docetaxel had improved OS (hazard ratio: 0.86; 95% CI, 0.75 to 0.98). Median OS was 10.5 months on the ramucirumab plus docetaxel arm versus 9.1 months on the placebo plus docetaxel arm. Median progression free survival was 4.5 months for the ramucirumab arm compared to 3 months in the control arm (hazard ratio: 0.76; 95% CI, 0.68 to 0.86). Objective response rate was 22.9% for the ramucirumab arm (95% CI, 19.7% to 26.4%) compared to 13.6% in the control arm (7).

Ramucirumab 10 mg/kg Q3W in combination with docetaxel is approved to treat metastatic NSCLC. Additionally, ramucirumab 8 mg/kg administered Q2W is approved to treat other advanced cancers: as a single agent or in combination with paclitaxel for gastric or gastro-esophageal junction adenocarcinoma, and in combination with a FOLFIRI regimen for CRC. The dosing schedule selected for this study is supported by efficacy data from studies with tusamitamab ravtansine 100 mg/m^2 Q2W (see Investigator's Brochure for tusamitamab ravtansine) and the Q2W dosing schedule for ramucirumab approved for other cancer indications (see Cyramza® prescribing information).

Combined ICI and VEGF/VEGF receptor inhibition have shown benefit in multiple tumor types through immune modulation. Pembrolizumab and ramucirumab (P+R) were evaluated in patients with advanced, ICI-exposed, in a substudy of Lung-MAP1, a master protocol for patients with Stage IV previously treated NSCLC. In this randomized, Phase II study from the Lung-MAP platform,136 patients were randomized to receive pembrolizumab + ramucirumab or the Investigator's choice of standard therapeutic regimens (SOC). Ramucirumab 10 mg/kg and pembrolizumab 200 mg Q3W were used. Overall survival (OS) was significantly improved with P+R compared to SOC: median (95% CI) OS was 14.5 (13.9 to 16.1) months for P+R: and 11.6 (9.9 to 13.0) months for SOC (HR: 0.69 [0.51 to 0.92], P value from the standard log-rank test equal to 0.05 and 0 .15 from the weighted log-rank test). Neither progression-free survival (PFS) or objective response rate (ORR) differed between the treatment arms (2).

Addition of pembrolizumab could be a new option for the treatment of advanced NSQ NSCLC after platinum and ICI. A new cohort of 6 to 12 patients will be added to this protocol in order to assess the safety of this tri-therapy (tusamitamab ravtansine-ramucirumab-pembrolizumab) and validate the dose of tusamitamab ravtansine to be used in case of further development of this combination in this indication.

The balance of anticipated benefits and the reported risks of tusamitamab ravtansine identified in ongoing studies TED13751 and TCD15054 supports its continued clinical development, both as monotherapy and in combination regimens with chemotherapy and immunotherapy agents. Given the considerable risks of adverse effects including neutropenia, anemia, and infection associated with docetaxel, the combination of tusamitamab ravtansine with ramucirumab may represent a treatment regimen with an improved safety profile as compared to the approved combination of docetaxel and ramucirumab.

The combination of tusamitamab ravtansine with ramucirumab with or without pembrolizumab will provide efficacy and safety data in patients with CEACAM5-positive (CEACAM5 ≥50%) NSQ NSCLC tumors.

2.2 BACKGROUND

Lung cancer is one of the most commonly diagnosed cancers and is the leading cause of cancer-related mortality worldwide (8). Non-small-cell lung cancer (NSCLC) accounts for 85% of all lung cancers (9) and comprises several histopathological subtypes, of which adenocarcinoma (60%) and squamous-cell carcinoma (15%) are the most common (10).

The majority of patients with NSCLC presents an advanced stage at the time of diagnosis. These patients have a median overall survival (OS) of up to 8 to 12 months (11), and in 2015, a 5 year survival rate of approximately 25% (12) About 15% to 20% of patients with NSCLC have tumors with key genomic alterations that are amenable to targeted therapy, which include epidermal growth factor receptor (*EGFR*) mutations and ROS receptor tyrosine kinase 1 (*ROS1)* and anaplastic lymphoma kinase (*ALK*) rearrangements (13).

Until recently the only available treatment option for advanced or metastatic NSQ NSCLC lacking 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 (14). The standard second-line treatment for NSCLC has been docetaxel (15); docetaxel's activity was found to be enhanced by the addition of ramucirumab (7).

More recently, immunotherapy has initiated 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 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 (16, 17, 18, 19), however only small subset (20% to 30%) of patients responds to these treatments. Despite improvement in outcomes with newer lines therapy, including anti-PD -1/PD -L1 antibodies, the disease often progresses. Additional therapeutic approaches are needed to improve the clinical efficacy and health-related quality of life (HRQOL) in patients with advanced/metastatic NSCLC.

2.3 BENEFIT/RISK ASSESSMENT

To date, efficacy and safety data from ongoing studies of tusamitamab ravtansine (TED13751, TCD15054, ACT16146, ACT16444, ACT16525, ACT16432 and EFC15858) support continued clinical development of tusamitamab ravtansine. Information about the known and expected benefits, risks, and reasonably anticipated AEs with tusamitamab ravtansine may be found in the Investigator's Brochure (IB). Based on available safety data, the main anticipated risk to patients is corneal toxicity presenting as microcystic keratopathy/keratitis, which is reversible and manageable with dose delay and dose reduction in some patients. Peripheral neuropathy is an identified risk.

Other potential risks include colitis (including hemorrhagic), cardiotoxicity (myocardial or conduction abnormalities), hematologic cytopenia, and hepatotoxicity, as well as systemic acute hypersensitivity (including anaphylaxis) and, in patients who received tusamitamab ravtansine in peripheral veins, local infusion site reactions to tusamitamab ravtansine (6).

Ramucirumab, a human IgG1 monoclonal antibody that inhibits VEGFR-2, is approved in combination with docetaxel for the treatment of patients with metastatic NSCLC. Given the considerable risks of adverse effects including neutropenia, anemia, and infection associated with docetaxel, the combination of tusamitamab ravtansine with ramucirumab may represent a treatment regimen with an improved safety profile as compared to the approved combination of docetaxel and ramucirumab. More detailed information about the known and expected benefits and risks and reasonably expected adverse effects of ramucirumab may be found in the US Package Insert or Summary of Product Characteristics for Cyramza®.

Besides targetable genetic alterations, also the expression of PD-L1, an immune suppressive molecule, needs to be considered for therapeutic decision-making. The PD-1 immune checkpoint inhibitor (ICI) pembrolizumab has been shown to have higher efficacy as first-line treatment compared with platinum-based chemotherapy in patients without the presence of a driver oncogene alteration but PD-L1 expression in at least 1% of tumor cells (TPS ≥1%) (1). Pembrolizumab, as monotherapy, is approved for the first-line treatment of patients with Stage III NSCLC, who are not candidates for surgical resection or definitive chemoradiation, or metastatic NSCLC whose tumors express PD-L1 with a TPS ≥50% as determined by an approved test, with no EGFR or ALK genomic tumor aberrations. Extension of indication was recently (April 2019) given in the US by the FDA to patients for whom TPS is ≥1%. This approval was based on the results of a Phase 3, randomized trial of 1274 patients with untreated locally advanced or metastatic NSCLC without EGFR or ALK mutations and with PD-L1 TPS ≥1% (1). Patients were randomized to receive either pembrolizumab or chemotherapy. The primary endpoint was overall survival (OS). Overall survival was significantly longer in the pembrolizumab group than in the chemotherapy group in all three TPS populations (TPS ≥50% hazard ratio 0.69, 95% CI 0.56-0.85, p=0.0003; TPS ≥20% 0.77, 0.64-0.92, p=0.0020; and TPS ≥1% 0.81, 0.71-0.93, p=0.0018). The median survival values by TPS population were 20.0 months (95% CI 15.4-24.9) for pembrolizumab versus 12.2 months (10.4-14.2) for chemotherapy, 17.7 months (15.3-22.1) versus 13.0 months (11.6-15.3), and 16.7 months (13.9-19.7) versus 12.1 months (11.3-13.3), respectively. In the PD-L1 TPS ≥50% population, 118 (39%, 95% CI 34-45) of 299 patients in the pembrolizumab group and 96 (32%, 95% CI 27-38) of 300 patients in the chemotherapy group had an objective response to treatment. The values in the TPS ≥20% and ≥1% populations were 138 (33%, 95% CI 29-38) of 413 versus 117 (29%, 95% CI 25-34) of 405 and 174 (27%, 95% CI 24-31) of 637 versus 169 (27%, 95% CI 23-30) of 637, respectively (1, 20).

Pembrolizumab in combination with chemotherapy is approved for the first-line treatment of patients with metastatic NSQ NSCLC, with no *EGFR* or *ALK* genomic tumor aberrations. This approval was based on the results of a Phase 3 double-blind, randomized (in a 2:1 ratio) trial of 616 patients who had received no previous treatment for metastatic disease to receive pemetrexed and a platinum-based drug plus either 200 mg of pembrolizumab or placebo every 3 weeks for 4 cycles, followed by pembrolizumab or placebo for up to a total of 35 cycles plus pemetrexed maintenance therapy (21). Improvement in OS was seen across all PD-L1 categories that were evaluated. Median progression-free survival was 8.8 months (95% CI 7.6 to 9.2) in the

pembrolizumab-combination group and 4.9 months (95% CI, 4.7 to 5.5) in the placebo-combination group (hazard ratio for disease progression or death: 0.52, 95% CI 0.43 to 0.64, p <0.001). The response rate as assessed by blinded, independent central radiologic review was 47.6% (95% CI 42.6 to 52.5) in the pembrolizumab-combination group and 18.9% (95% CI, 13.8 to 25.0) in the placebo-combination group (p <0.001).

The combination of tusamitamab ravtansine with an immune-checkpoint inhibitor (ICI) or the standard of care (SOC) should improve the outcome, with a better tolerability for triplet combination, and without additional toxicity as no overlap is expected.

Safety data were collected so far with tusamitamab ravtansine and pembrolizumab combination in the ACT16146 study. Based on the patients treated as of 17 June 2022, the combination cohorts at the suggested dose of tusamitamab ravtansine 150 mg/m^2 have all been well tolerated.

2.3.1 Overall benefit: risk conclusion

To date, efficacy and safety data from ongoing studies of tusamitamab ravtansine (TED13751 and TCD15054) support continued clinical development of tusamitamab ravtansine. The combination of tusamitamab ravtansine with ramucirumab may represent a treatment regimen with an improved safety profile as compared to the combination of docetaxel with ramucirumab approved for the treatment of advanced NSCLC.

Addition of pembrolizumab could be a new option for the treatment of advanced NSQ NSCLC after platinum and ICI.

3 OBJECTIVES AND ENDPOINTS

Table 3 - Objectives and endpoints

Doublet cohort

Objectives	Endpoints
Primary	
• **Part 1 (safety run-in):** To assess the tolerability and to confirm the recommended dose of tusamitamab ravtansine in combination with ramucirumab in the NSQ NSCLC population	• **Part 1:** Incidence of study drug-related dose-limiting toxicity (DLT) at Cycle 1 and Cycle 2 (C1D1 to C2D14). Anticipated DLT includes, but is not limited to, corneal toxicity
• **Part 2:** To assess the antitumor activity of tusamitamab ravtansine in combination with ramucirumab in the NSQ NSCLC population	• **Part 2:** Objective response rate (ORR) defined as proportion of participants with confirmed complete response (CR) or partial response (PR) as best overall response (BOR) determined per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.
Secondary	
• To assess the safety and tolerability of tusamitamab ravtansine in combination with ramucirumab	• Incidence of treatment emergent adverse events (TEAEs) and serious adverse events (SAEs) and laboratory abnormalities according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) V5.0
• To assess the durability of the response to treatment with tusamitamab ravtansine in combination with ramucirumab	• Duration of response (DOR), defined as the time from first documented evidence of CR or PR until progressive disease (PD) determined per RECIST v1.1 or death from any cause, whichever occurs first
• To assess anti-tumor activity of tusamitamab ravtansine in combination with ramucirumab on progression free survival (PFS) and disease control rate (DCR)	• Progression-free survival, defined as the time from the first investigational medicinal product (IMP) administration to the date of the first documented disease progression or death due to any cause, whichever comes first • Disease control rate (DCR), defined as the percentage of participants who have achieved confirmed CR, confirmed PR or stable disease as per RECIST v1.1
• To assess the pharmacokinetic (PK) profiles of tusamitamab ravtansine (SAR408701) and ramucirumab when given in combination	• Pharmacokinetic parameters of tusamitamab ravtansine (SAR408701) and ramucirumab
• To assess the immunogenicity of tusamitamab ravtansine (SAR408701) when given in combination with ramucirumab	• Incidence of anti-therapeutic antibodies (ATAs) against tusamitamab ravtansine (SAR408701)

Objectives	Endpoints
Tertiary/Exploratory	
• To explore circulating carcinoembryonic antigen (CEA) as a potential biomarker for activity and to evaluate circulating CEA levels at prescreening	• Circulating CEA at prescreening, screening, and during the treatment period

Abbreviations: ATA=antitherapeutic antibody; BOR=best overall response; CEA=carcinoembryonic antigen; CR=complete response; DLT=dose-limiting toxicity; DCR=disease control rate; DOR=duration of response; IMP=investigational medicinal product; NCI CTCAE= National Cancer Institute Common Terminology Criteria for Adverse Events; NSQ NSCLC=non-squamous, non small-cell lung cancer; PD=progressive disease; PFS=progression-free survival; PK=pharmacokinetic; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors.

Triplet cohort

Objectives	Endpoints
Primary	
• To assess the tolerability and to confirm the recommended dose of tusamitamab ravtansine in combination with ramucirumab and pembrolizumab in the NSQ NSCLC population	• Incidence of study drug-related dose-limiting toxicity (DLT) at Cycle 1 (C1D1 to C1D21). Anticipated DLT includes, but is not limited to, corneal toxicity.
Secondary	
• To assess the safety and tolerability of tusamitamab ravtansine in combination with ramucirumab and pembrolizumab	• Incidence of treatment emergent adverse events (TEAEs) and serious adverse events (SAEs) and laboratory abnormalities according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) V5.0
• To assess the antitumor activity of tusamitamab ravtansine in combination with ramucirumab and pembrolizumab in the NSQ NSCLC population	• Objective response rate (ORR) defined as proportion of participants with confirmed complete response (CR) or partial response (PR) as best overall response (BOR) determined per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
• To assess the immunogenicity of tusamitamab ravtansine (SAR408701) when given in combination with ramucirumab and pembrolizumab	• Incidence of anti-therapeutic antibodies (ATAs) against tusamitamab ravtansine (SAR408701)
Tertiary/Exploratory	
• To explore circulating carcinoembryonic antigen (CEA) as a potential biomarker for activity and to evaluate circulating CEA levels at prescreening	• Circulating CEA at prescreening, screening, and during the treatment period

Abbreviations: ATA=antitherapeutic antibody; BOR=best overall response; CR=complete response; DLT=dose-limiting toxicity; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; NSQ NSCLC=non-squamous, non small-cell lung cancer; PK=pharmacokinetic; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors.

3.1 APPROPRIATENESS OF MEASUREMENTS

Each of the efficacy and safety 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 2, open-label, multi-center study assessing safety, efficacy (antitumor activity), and PK of the combination of tusamitamab ravtansine and ramucirumab in metastatic CEACAM5-positive (defined as CEACAM5 IHC intensity ≥2+ in ≥50% of tumor cells) in patients with non-squamous, non–small-cell lung cancer (NSQ NSCLC) participants previously treated with platinum-based chemotherapy and an immune checkpoint inhibitor.

In the **prescreening phase,** patients with NSQ NSCLC will have tumor tissue tested centrally to assess proportions of CEACAM5-positive cells and intensity of expression, with a prospective analysis of CEACAM5 expression on 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 may confirm that available material is sufficient 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 a participant may be on prior anticancer therapy.

Once the results for CEACAM5 available, only participants with positive results (defined as CEACAM5 expression of ≥2+ in intensity involving at least 50% of the tumor cell population), in archival tumor sample (or if not available fresh biopsy sample) will enter in **screening phase**. During the screening phase, all inclusion/exclusion criteria will be checked to confirm the participants' eligibility for **treatment** part.

Once the participant is screened, the participant may be determined to be eligible for a **treatment phase** comprising 2 cohorts (doublet cohort and triplet cohort)

<u>The doublet cohort is a 2-parts study:</u>

Part 1 (Safety Run-In): In Part 1, participants will be treated with tusamitamab ravtansine and ramucirumab to assess the tolerability of the combination to be used in the subsequent part of the study. The first 3 participants will receive ramucirumab at 8 mg/kg followed by tusamitamab ravtansine at 100 mg/m^2 every 2 weeks (Q2W). Administration of tusamitamab ravtansine will begin at least 1 hour after completion of ramucirumab infusion.

The DLT observation period is the first 2 cycles (approximately 28 days). A DLT-evaluable participant must have completed 2 cycles of treatment or have been discontinued from study treatment because of a DLT; DLT non-evaluable participants will be replaced.

A minimum delay of 1 week is required between the initial dose in the first participant treated in a DL cohort and dosing the next 2 participants treated at the same DL.

- If ≤1/3 participants treated at the starting dose experiences a DLT, 3 additional participants will be treated to confirm the tolerability of the combination.
  - If ≤1/6 participants treated at the starting dose experiences a DLT, the starting dose will be the RP2D.
  - If ≥2/6 participants treated at the starting dose experience DLTs, the dose will be de-escalated to DL -1.
- If ≥2/3 participants treated at the starting dose experience DLTs, the dose will be de-escalated to DL minus 1 (DL -1).
- If ≤1 of the first 3 participants treated at DL -1 experiences a DLT, 3 additional participants will be treated at this DL.
  - If ≤1/6 participants treated at DL -1 experiences a DLT, DL-1 will be the RP2D.
  - If ≥2/6 participants treated at DL -1 experience a DLT, an alternative dosage might be considered or the doublet cohort may be stopped.
- If ≥2/3 participants treated at DL -1 experience a DLT, an alternative dosage might be considered or the doublet cohort may be stopped.

Note: if ≥2/6 or ≥2/3 participants treated at DL -1 experience DLTs, an alternative dosage might be considered from a safety viewpoint by the Sponsor after consulting with SC. Dose reduction is shown in Table 4.

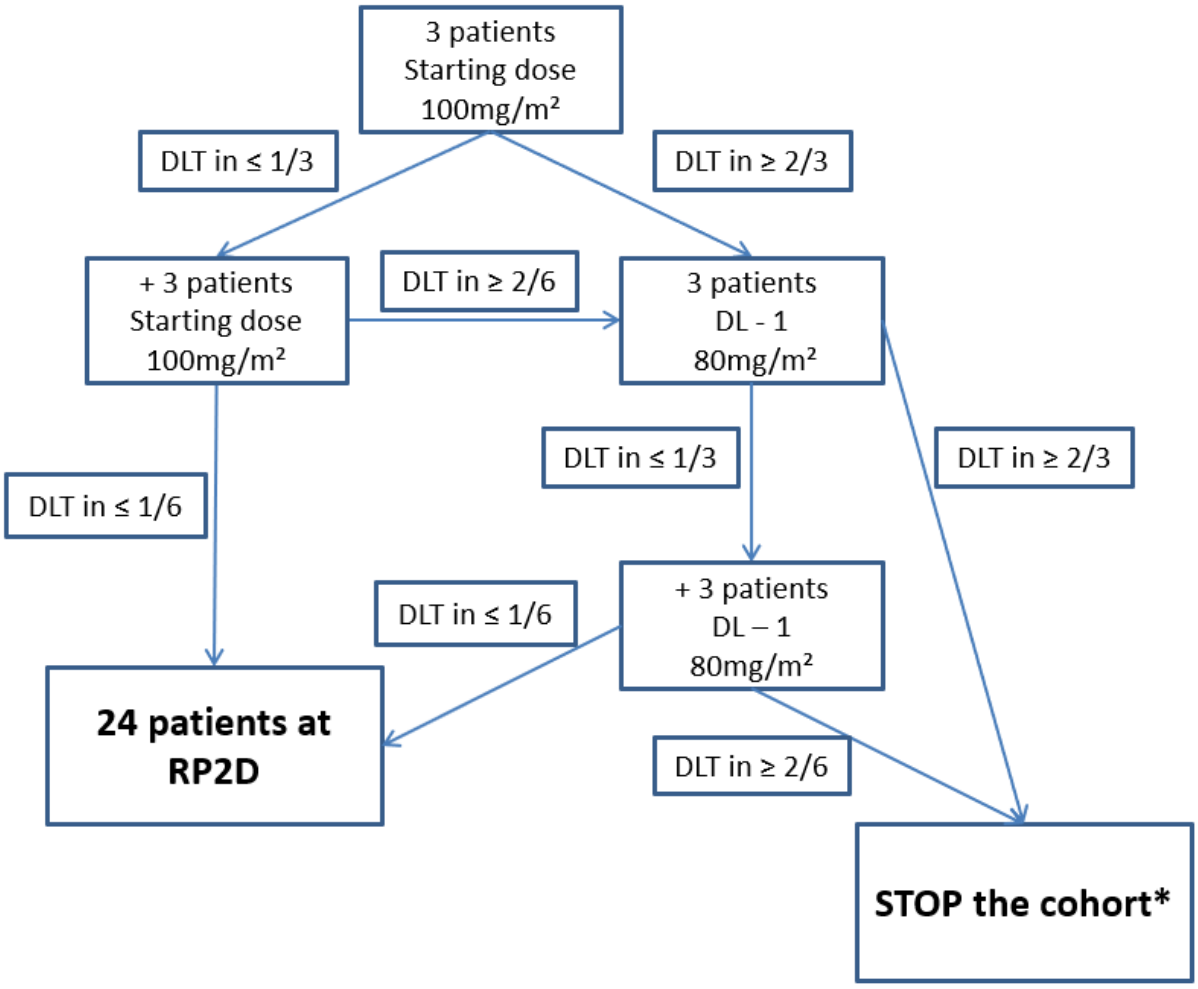
Table 4 - Dose reduction for the doublet cohort Part 1 (safety run-in)

Dose level (DL)	tusamitamab ravtansine	Ramucirumab
Starting dose	100 mg/m^2 Q2W	8 mg/kg Q2W
Minus -1 (DL-1)	80 mg/m^2 Q2W	8 mg/kg Q2W

DL=dose level; Q2W=every 2 weeks.
Infusion of tusamitamab ravtansine will be administered at least 1 hour after the end of ramucirumab infusion. For patients with a BSA >2.20 m^2, the tusamitamab ravtansine dose will be calculated based on a BSA of 2.20 m^2.

The decision tree for doses in Part 1 is summarized in Figure 4.

Figure 4 - Decision tree for the doublet cohort Part 1 for tusamitamab ravtansine



*Note: In case of 2 or more DLTs at DL -1, the cohort may be stopped or the dosage reconsidered.
Abbreviations: DL -1=dose level -1 (80 mg/m²); DLT=dose-limiting toxicity; RP2D=recommended dose.

Following the identification of the RP2D, Part 2 of the study will be initiated.

Dose limiting toxicity definition

All AEs specified in Table 5 occurring during the first 2 cycles of treatment, unless due to disease progression or to a cause obviously unrelated to IMP, will be considered DLTs. The duration of the DLT observation period will be longer for a participant who delays initiation of Cycle 2 due to a treatment-related AE for which the event's duration would determine whether the AE meets the definition of a DLT. The NCI CTCAE version 5.0 will be used to assess the severity of AEs. Causal relationships are to be determined by the Investigator. The DLTs will be confirmed by the SC.

Table 5 - Dose-limiting toxicities

Hematological abnormalities
Grade 4 neutropenia for 7 or more consecutive days
Grade 3 to 4 neutropenia complicated by fever (temperature ≥38.5°C on more than 1 occasion) or microbiologically or radiographically documented infection
Grade ≥3 thrombocytopenia associated with clinically significant bleeding requiring clinical intervention
Non-hematological abnormalities
Elevated urine protein ≥3 g/24 h
Grade 4 non-hematologic AE
Grade ≥3 keratopathy
Grade 4 or refractory hypertension
In addition, any other AE that the recruiting Investigators and Sponsor deem to be dose limiting, regardless of its grade, may also be considered as DLT.

Part 2: It is planned that 30 treated patients will be evaluable for response (the 6 patients from the safety run-in treated at the recommended dose will be included). During the treatment period, participants will have tumor assessments every 8 weeks.

After the EOT visit, the **Follow-up** (FU) **visit** will be performed at 90 (±7) days after the last infusion. During the FU visit, the participants will be monitored for all ongoing related AEs and all SAEs and AESIs, regardless of relationship until resolution or stabilization (ie, an event ongoing without any change for at least 3 months). All new related AEs, SAEs, or AESIs will be followed until resolution or stabilization. If ongoing IMP-related AEs and all SAEs/AESIs are resolved or stabilized, no further safety follow-up visit will be needed; if not resolved or stabilized, an on-site follow-up visit will be performed every 12 weeks (±7 days) until resolution or stabilization.

For the doublet cohort, a participant who stopped treatment for a reason other than PD, follow-up visits will be performed every 12 weeks (±7 days) after the last tumor assessment until documented radiological disease progression, start of a new anticancer therapy, death, study cut-off date of the secondary ORR endpoint of the triplet cohort, or withdrawal of participant's consent (whichever comes first).

The study cut-off for the primary ORR endpoint analysis corresponds to the date on which all evaluable treated patients have had at least 2 postbaseline tumor assessments, experienced confirmed objective response, or have discontinued the study for any reason; the study cut-off can be up to approximately 6 months (4 months for 2 assessments, with an additional 2 months if confirmation of a response is needed) from the date the last participant's first administration.

After the study cut-off date for the primary ORR analysis, if clinical benefit is observed, a patient still receiving study treatment can continue study treatment until PD, unacceptable toxicity, or withdrawal of participant's consent, and will continue to undergo all assessments as per the study flow chart.

Triplet cohort:

Participants will be treated with tusamitamab ravtansine and ramucirumab and pembrolizumab to assess the tolerability of the combination to be used in the subsequent studies. The first 3 participants will receive ramucirumab at 10 mg/kg followed by tusamitamab ravtansine at 150 mg/m^2 and pembrolizumab at 200 mg every 3 weeks (Q3W). Administration of tusamitamab ravtansine will begin at least 1 hour after completion of ramucirumab infusion.

DLT definition is reported in Table 5.

The DLT observation period is the first cycle (approximately 21 days). A DLT-evaluable participant must have completed 1 cycle of treatment or have been discontinued from study treatment because of a DLT. DLT non-evaluable participants will be replaced.

A minimum delay of 1 week is required between the initial dose in the first participant treated in a DL cohort and dosing the next 2 participants treated at the same DL.

- If ≤1/3 participants treated at the starting dose experiences a DLT, 3 additional participants will be treated to confirm the tolerability of the combination.
  - If ≤1/6 participants treated at the starting dose experiences a DLT, the starting dose will be the RP2D.
  - If ≥2/6 participants treated at the starting dose experience DLTs, the dose will be de-escalated to DL -1.
- If ≥2/3 participants treated at the starting dose experience DLTs, the dose will be de-escalated to DL minus 1 (DL -1).
- If ≤1 of the first 3 participants treated at DL -1 experiences a DLT, 3 additional participants will be treated at this DL.
  - If ≤1/6 participants treated at DL -1 experiences a DLT, DL-1 will be the RP2D.
  - If ≥2/6 participants treated at DL -1 experience a DLT, an alternative dosage might be considered or the triplet cohort may be stopped.
- If ≥2/3 participants treated at DL -1 experience a DLT, an alternative dosage might be considered or the triplet cohort may be stopped.

Note: if ≥2/6 or ≥2/3 participants treated at DL -1 experience DLTs, an alternative dosage might be considered from a safety viewpoint by the Sponsor after consulting with SC. Dose reduction is shown in Table 6.

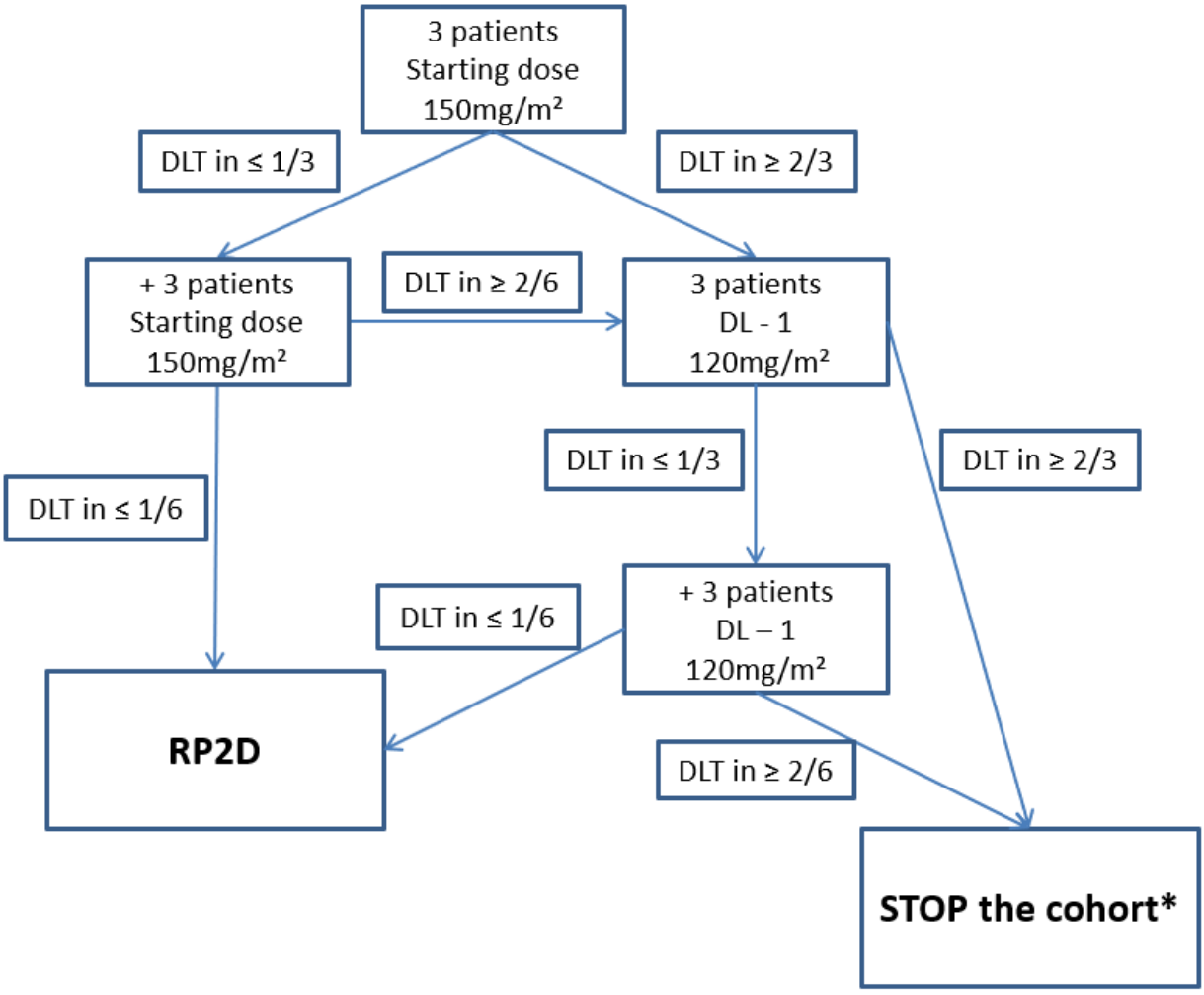
Table 6 - Dose reduction for the triplet cohort

Dose level (DL)	tusamitamab ravtansine	ramucirumab	pembrolizumab
Starting dose	150 mg/m² Q3W	10 mg/kg Q3W	200 mg Q3W
Minus -1 (DL-1)	120 mg/m² Q3W	10 mg/kg Q3W	200 mg Q3W

DL=dose level; Q3W=every 3 weeks.
Infusion of tusamitamab ravtansine will be administered at least 1 hour after the end of ramucirumab infusion. For patients with a BSA >2.20 m², the tusamitamab ravtansine dose will be calculated based on a BSA of 2.20 m².

The decision tree for doses for triplet cohort is summarized in Figure 5.

Figure 5 - Decision tree for the triplet cohort for tusamitamab ravtansine



*Note: In case of 2 or more DLTs at DL -1, the cohort may be stopped or the dosage reconsidered.
Abbreviations: DL -1=dose level -1 (120 mg/m²); DLT=dose-limiting toxicity; RP2D=recommended dose.

The study cut-off for the secondary ORR endpoint analysis of triplet cohort corresponds to the date on which all evaluable treated patients have had at least 2 post baseline tumor assessments, experienced confirmed objective response, or have discontinued the study for any reason. This study cut-off will occur approximately 4.5 months after the date of the first IMP administration of the last participant: 3 months for 2 tumor assessments and 1.5 months if a confirmation of response is needed.

Disclosure Statement:

This is an open-label, single-arm, 2 cohorts study in patients with previously treated metastatic NSQ NSCLC.

Number of participants:

In the doublet cohort, approximately 225 participants will be prescreened (CEACAM5 prescreening failure rate is 80% and study screen failure rate is 20%) to achieve up to approximately 36 treated participants.

In the triplet cohort, approximately 74 participants will be prescreened to achieve up to approximately 12 DLT evaluable participants, based on the doublet cohort CEACAM5 prescreening failure rate of 79% and an estimated study screen-failure rate of 23%.

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, enrolled participants may receive study intervention until disease progression, unacceptable AE, or the participant's or investigator's decision to stop the treatment. Each cycle of treatment will have a duration of 2 weeks in the doublet cohort and 3 weeks in triplet cohortAfter discontinuing study intervention, participants will return to the study site approximately 30 (±5) days after the last IMP administration or before the participant receives another anticancer therapy, whichever is earlier, for end-of-treatment assessments; additionally, a final safety follow-up visit will be scheduled 90 days after the last dose of IMP. The expected duration of study intervention for participants may vary, based on progression date; median expected duration of study per participant is estimated as 11 months (1 month for screening, a median of 6 months for treatment, and a median of 4 months for end-of-treatment follow-up). The total estimated duration of enrollment will be approximately 12 months.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Based on histology, therapy and prognosis, lung cancer is divided into two 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: non-squamous carcinoma (including adenocarcinoma, large-cell carcinoma and other subtypes) and squamous cell (epidermoid) carcinoma. Adenocarcinoma is the most common subtype of NSQ-NSCLC (17).

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 (22).

Accurate pathologic assessment with tumor mutation profiling and staging are essential for treatment decisions. In general, systemic therapy is recommended for patients with metastatic (Stage IV) disease, especially in disseminated metastasis. Appropriate systemic therapy choice 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 has been considered the gold standard, with evidence of improved survival and symptom control, and superior quality of life compared to best supportive care. After improvement of biomarker testing for genetic alterations in tumor cells, the number of available targeted therapies has been increasing, and targeted therapy has been shown to decrease tumor burden, decrease symptom and dramatically improve the quality of life for patient with specific genetic alteration.

Doublet chemotherapy regimens are recommended as first line chemotherapy for NSQ NSCLC patients whose tumor has negative *ALK* and *ROS1* re-arrangement or sensitizing *EGFR* mutations and with 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-checkpoint inhibitors are recommended as subsequent therapy for all patients, based on reported improvement in survival, longer response duration, and a better safety profile compared to chemotherapy. Current data suggest that patients with *EGFR* mutations or *ALK* rearrangement have low response rates to PD-1 or PD-L1 inhibitors when compared to patients without these alterations; therefore checkpoint inhibitors are not considered as recommended subsequent treatment in patients with these alterations.

Since ramucirumab has shown activity in combination with docetaxel in the REVEL study (7), it is anticipated that ramucirumab combined with tusamitamab ravtansine should also show antitumor activity in advanced NSQ NSCLC. Due to the different mechanisms of action of tusamitamab ravtansine and ramucirumab, their combination should have better efficacy than either agent alone, and based on lack of anticipated PK interaction, should have similar safety profiles to those with either monotherapy. Because tusamitamab ravtansine's safety profile differs from that of docetaxel, it is expected that the safety of a ramucirumab/tusamitamab ravtansine combination will be improved compared to the combination of ramucirumab with docetaxel currently approved to treat advanced NSCLC.

4.3 DOSE JUSTIFICATION

In the dose-escalation phase of first-in-human study TED13751 exploring 5 to 150 mg/m^2 tusamitamab ravtansine doses administered once every 2 weeks, the recommended dose was determined to be 100 mg/m^2 administered every 2 weeks. A cohort of patients with heavily pretreated, CEACAM5-positive, NSQ NSCLC ongoing in TED13751 are receiving tusamitamab ravtansine at the recommended dose of 100 mg/m^2 every 2 weeks. Results from the 64 treated and evaluable patients from this cohort showed encouraging antitumor activity in the subset with NSQ

NSCLC tumors that were ≥50% positive for CEACAM5 expression (6). This antitumor activity was associated with a response rate of 20.3% (95% CI, 12.3% to 31.7%) per RECIST v1.1 in the response-evaluable population.

As no overlap in the safety profiles for ramucirumab and for tusamitamab ravtansine is anticipated, the starting dose tested in the Part 1 of the study for tusamitamab ravtansine will be the MTD used in monotherapy, 100 mg/m^2 every 2 weeks. In the event of a safety concern, the dose will be decreased to 80 mg/m^2 every 2 weeks. Should a safety concern still exist despite a decrease in the dose, the study will be definitively stopped.

A fixed dose of ramucirumab will be administered. The dosage chosen for ramucirumab of 8 mg/kg Q2W has been approved as monotherapy for the treatment of pretreated hepatocellular carcinoma; as monotherapy or in combination with paclitaxel for the treatment of heavily pretreated advanced or metastatic gastric or gastroesophageal-junction adenocarcinoma; and in combination with FOLFIRI for the treatment of CRC. Therefore, extensive postmarketing clinical experience as well as registrational trials for these indications demonstrate both acceptable safety and tolerability of the 8 mg/kg Q2W regimen in heavily pretreated patients with advanced cancers, as well as potent antitumor activity. Because nonclinical studies do not predict an effect of tusamitamab ravtansine on ramucirumab metabolism or exposures, it is not anticipated that any adjustment to ramucirumab dosing will be required for the combination.

Combining ICI and VEGF/VEGF receptor inhibition have shown benefit in multiple tumor types through immune modulation. Pembrolizumab 200 mg iv and ramucirumab10mg/kg every 3 weeks (P+R) were evaluated in patients with advanced, ICI-exposed, in a substudy of Lung-MAP1, a master protocol for patients with Stage IV previously treated NSCLC. In this randomized, Phase II study from the Lung-MAP platform,136 patients were randomized to receive pembrolizumab + ramucirumab or the Investigator's choice of standard therapeutic regimens (SOC). Overall survival (OS) was significantly improved with P+R compared to SOC: median (95% CI) OS was 14.5 (13.9 to 16.1) months for P+R: and 11.6 (9.9 to 13.0) months for SOC (HR: 0.69 [0.51 to 0.92], P value from the standard log-rank test equal to 0.05 and 0 .15 from the weighted log-rank test). Neither progression-free survival (PFS) or objective response rate (ORR) differed between the treatment arms (2).

As of August 2022, a total of 20 patients were treated in the ACT16146 study. Preliminary encouraging signs of activity with the 3 regimens - tusamitamab ravtansine (SAR408701) combined with pembrolizumab and platinum-based chemotherapy with or without pemetrexed, have been observed. The combination of tusamitamab ravtansine with pembrolizumab, with or without chemotherapy, is feasible and well tolerated without new safety signal observed. Given the development of a dose limiting toxicity with 170 mg/m^2 and the association between exposure and development of ocular toxicity observed in first-in-human (FIH) study, as well as a lack of discernable difference in efficacy between 150 and 170 mg/m^2, 150 mg/m^2 has been chosen as the recommended dose for tusamitamab ravtansine in subsequent studies when combined with pembrolizumab with or without chemotherapy.

The starting dose for tusamitamab ravtansine is 150 mg/m^2 and was defined based on findings from first-in-human study TED13751. In this study, the RP2D for tusamitamab ravtansine given Q3W was 170 mg/m^2. Given that tusamitamab ravtansine exposure PK parameters at Cycle 1 of

administration as a single agent of 170 mg/m^2 Q2W were significantly associated with the occurrence of Grade ≥2 corneal events, it is anticipated that 150 mg/m^2 may result in less ocular toxicity, and overall will be better tolerated than 170 mg/m^2. In addition, this dose corresponds to the same dose intensity as with the recommended 100 mg/m² Q2W dose.

Based on the experience of the first patients treated in ACT16146 for the dosage of tusamitamab ravtansine and pembrolizumab and the experience of the doublet cohort, the starting dose for tusamitamab ravtansine will be 150 mg/m^2, ramucirumab 10 mg/kg and pembrolizumab 200 mg, every 3 weeks.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he/she has completed all phases of the study including the End of Treatment visit and the Follow-Up visit approximately 90 days after the last IMP administration. The end of the study is defined as the date of the last visit of the last participant in the study, or last scheduled procedure shown in the Schedule of Activities for the last participant in the trial globally.

5 STUDY POPULATION

Prospective approval of protocol deviations from 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 the following criteria apply:

Age

I 01. Participants 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 NSQ NSCLC.

I 03. Metastatic disease progression fulfilling both of the following 2 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 completing treatment will be considered as first-line treatment.
AND

b) Having progressive disease during or after 1 immune checkpoint inhibitor (anti-PD1/PD-L1); this could be given as monotherapy or in combination with platinum-based chemotherapy (whatever the order).

I 04. For a tumor genotype with a sensitizing *EGFR* mutation or *BRAF* mutation or *ALK/ROS* alteration, demonstrated disease progression while receiving approved treatment for that genotype in addition to platinum-based chemotherapy and immune checkpoint inhibitor.

I 05. Expression of CEACAM5 as demonstrated prospectively by a centrally assessed immunohistochemical (IHC) assay of ≥2+ in intensity involving at least 50% of the tumor cell population in archival tumor sample (or if not available fresh biopsy sample). At least 5 slides of formalin-fixed, paraffin embedded (FFPE) tumor tissue sectioned at a thickness of 4 µm are required. If less material is available, the patient could still be considered eligible after discussion with the Sponsor, who may assess and confirm that the available material is sufficient for key evaluations.

I 06. 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 07. Eastern Cooperative Oncology Group (ECOG) performance status 0-1.

Sex

I 08. All (male or female)

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

a) Male participants

A male participant must agree to use contraception (see Appendix 5, Section 10.5) during the intervention period and for at least 4 months after the last dose of study intervention.

b) 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 1 of the following conditions applies:

- Not a woman of child-bearing 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 09. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2 EXCLUSION CRITERIA

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

Medical conditions

E 01. Untreated brain metastases and history of leptomeningeal disease. Patients with previously treated brain metastases may participate provided they are stable (ie, without evidence of progression by imaging for at least 4 weeks prior to the first administration of study intervention, and any neurologic symptoms have returned to baseline); there is no evidence of new or enlarging brain metastases; and the patient does not require any systemic corticosteroids to manage brain metastases within 3 weeks prior to the first dose of study intervention.

E 02. Significant concomitant illness, including any severe medical condition that, 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 that 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 human immunodeficiency virus (HIV) disease requiring antiretroviral treatment; or active infection with 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 known positive result for antibodies to hepatitis C and known quantitative hepatitis C virus [HCV] RNA results greater than the lower limit of detection of the assay).

E 05. Non-resolution of any prior treatment-related toxicity to < Grade 2 according to NCI CTCAE V5.0, with the exception of alopecia, vitiligo, or active thyroiditis controlled with hormone replacement therapy.

E 06. Unresolved corneal disorder or any previous corneal disorder considered by an ophthalmologist to predict 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 are excluded.

E 07. Radiographic evidence of major airway or blood vessel invasion or intratumor cavitation, regardless of tumor histology.

E 08. History of uncontrolled hereditary or acquired arterial thrombotic disorder or history of aneurism.

E 09. Major surgery within 28 days prior to Day 1/first IMP infusion, or subcutaneous venous access device placement within 7 days prior to Day1. Postoperative bleeding complications or wound complications from a surgical procedure performed in the last 2 months.

E 10. History of gross hemoptysis (defined as bright red blood or ≥1/2 teaspoon or ≥2.5 mL) within 2 months before the first administration of study intervention.

E 11. Clinically relevant congestive heart failure (CHF; NYHA II-IV, or LVEF less than 50%) or symptomatic or poorly controlled cardiac arrhythmia.

E 12. Any arterial thrombotic event, including myocardial infarction, unstable angina, cerebrovascular accident, or transient ischemic attack, within 6 months before the first administration of study intervention.

E 13. Uncontrolled arterial hypertension (systolic ≥150 mmHg or diastolic ≥90 mmHg) despite standard medical management. A participant with systolic pressure >150 mmHg or diastolic pressure >90 mmHg is ineligible for the study.

E 14. Serious or nonhealing wound, skin ulcer, or bone fracture within 28 days before the first administration of study intervention.

E 15. Gastrointestinal (GI) perforation and/or fistulae within 6 months prior to first administration of study intervention.

E 16. Significant bleeding disorders, vasculitis, or Grade 3-4 gastrointestinal (GI) bleeding within 3 months before the first administration of study intervention.

E 17. Bowel obstruction, history or presence of inflammatory enteropathy or extensive intestinal resection Crohn's disease, ulcerative colitis, or chronic diarrhea.

E 18. Medical condition requiring concomitant administration of a medication with a narrow therapeutic window and metabolized by CYP_{450} (See Appendix 9, Section 10.9); and for which a dose reduction cannot be considered.

E 19. Medical conditions requiring concomitant administration of a 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 20. Concurrent treatment with any other anticancer therapy.

E 21. More than 1line previous chemotherapy in metastatic setting.

E 22. Prior treatment with ramucirumab or docetaxel.

E 23. Prior therapy targeting CEACAM5.

E 24. Prior maytansinoid treatment (DM1 or DM4 antibody-drug conjugate).

E 25. 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 26. Contraindication to use of corticosteroid premedication.

E 27. Current therapeutic anticoagulation with warfarin, low-molecular-weight heparin, or similar agents. Patients receiving prophylactic, low-dose anticoagulation therapy are eligible provided that the coagulation parameters defined in the inclusion criteria (INR $\leq$1.5 or PT $\leq$1.5 $\times$ ULN, and PTT/aPTT $\leq$1.5 $\times$ ULN) are met.

Prior/concurrent clinical study experience

E 28. Previous enrollment in this study, current participation in any other clinical study involving an investigational study treatment, or any other type of medical research.

Diagnostic assessments

E 29. Poor organ function as defined by any one of the following prior to IMP administration:

a) Serum creatinine >1.5 × upper limit of normal (ULN) or 1.0 to 1.5 × ULN with estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 as estimated using a Modification of Diet in Renal Disease (MDRD) formula.

b) Total bilirubin >1.0 × ULN.

aspartate aminotransferase (AST), alanine aminotransferase (ALT) >2.5 × ULN
or
AST, ALT >5 x ULN in case of documented liver metastasis
or
AST, ALT >1.5 × ULN concomitant with alkaline phosphatase (ALP) >2.5 × ULN.
ALP >5 × ULN with normal ALT/AST, for patients with bone metastases.

c) Neutrophils <1.5 × 10^9/L
or
platelet count <100 × 10^9/L
or
hemoglobin <9 g/dL (blood infusion-free for at least 2 weeks).

E 30. Urine dipstick or routine analysis indicating proteinuria of 2+ or higher, unless a 24 hour urine collection demonstrates <1000 mg of protein.

Other exclusions

E 31. Individuals accommodated in an institution because of regulatory or legal order; prisoners or subjects who are legally institutionalized.

E 32. Any country-related specific regulation that would prevent the subject from entering the study - see Appendix 8: Country-specific requirements (Section 10.8).

E 33. 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 34. Participants are dependent on the Sponsor or Investigator (in conjunction with Section 1.61 of the ICH-GCP Ordinance E6).

E 35. 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 36. Any specific situation during study implementation/course that may rise ethics considerations.

E 37. Sensitivity to any of the study interventions, or components thereof, or drug or other allergy that, in the opinion of the Investigator, contraindicates participation in the study.

Triplet cohort exclusions

E 38. History of active autoimmune disease that has required systemic treatment in the past 2 years.

E 39. History of allogeneic tissue/solid organ transplantation.

E 40. Active infection requiring IV systemic therapy within 2 weeks prior to first study intervention administration or active tuberculosis.

E 41. Interstitial lung disease or history of pneumonitis that has required oral or IV steroids.

E 42. Symptomatic herpes zoster within 3 months prior to screening.

E 43. Significant allergies to humanized monoclonal antibodies.

E 44. Any radiation therapy to lung >30 Gy within 6 months of first study intervention administration.

E 45. Has received or will receive a live vaccine within 30 days prior to the first study intervention administration.

E 46. Thyroid-stimulating hormone (TSH) out of normal limits. If TSH is not within normal limits at baseline, the subject may still be eligible if T3 and free T4 are within the normal limits

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 assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure reasons, eligibility criteria, and any SAE.

For an individual who does not meet the criteria for participation in this study (screen failure) and for whom resolution of the screen failure may not be expected within a reasonable time frame, the screen failure will be recorded. Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened participants should be assigned a new participant number different from that assigned for the initial screening, and all the screening procedures will be repeated and entered in the screening visit pages. Participants who screen failed and then rescreen need to re-sign a new ICF. In the case that the participant is

a temporary screen failure (ie, requirement of a prolongation of the screening period), there is no need to have participant sign a new ICF if the participant finally participates in the trial. However, if the reason for the temporary screen failure is a reason that might have altered the participant's initial given agreement to participate, the Investigator should ask the participant to confirm willingness to continue or repeat some screening procedures and to participate in the trial. This oral agreement should be documented in the participant's chart. All the tests repeated outside of the protocol-specified window for the screening period should be repeated and entered to the additional pages.

5.5 CRITERIA FOR TEMPORARILY DELAYING PRESCREENING, SCREENING, STUDY INTERVENTION, STUDY PROCEDURES

During a regional or national emergency declared by a governmental agency, if the site is unable to adequately follow protocol mandated procedures, contingency measures are proposed in Appendix 11 (Section 10.11: Contingency measures for a regional or national emergency that is declared by a governmental agency) should be considered for prescreening, screening, study intervention, and study procedures.

6 STUDY INTERVENTIONS

6.1 STUDY INTERVENTIONS ADMINISTERED

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

Study drugs to be administered for doublet cohort are detailed in Table 7.

Table 7 - Overview of study interventions administered - Doublet cohort

Enter Arm Name (single arm)	tusamitamab ravtansine	ramucirumab
Type	Drug/Biologic	Biologic
Dose formulation	Concentrated solution for IV	Concentrated solution for IV
Unit dose strength(s)	5 mg/mL	10 mg/mL
Dosage level(s)	100 (80) mg/m^2 every 2 weeks	8 mg/kg every 2 weeks
Route of administration	IV infusion	IV infusion
IMP (single-arm)	IMP	IMP
Packaging and labeling	Supplied in a 30 mL glass vial with a plastic flip-off cap, containing 125 mg/25 mL tusamitamab ravtansine, and labelled with a multilingual booklet	Supplied in a single-dose vial (100 mg/10 mL or 500 mg/50 mL) individually packaged in a carton.
[Current/Former name(s) or alias(es)]	None	Cyramza

Study drugs to be administered for triplet cohort are detailed in Table 8.

Table 8 - Overview of study interventions administered - Triplet cohort

Enter Arm Name (single arm)	tusamitamab ravtansine	ramucirumab	pembrolizumab
Type	Drug/Biologic	Biologic	Biologic
Dose formulation	Concentrated solution for IV	Concentrated solution for IV	Concentrate for solution for infusion
Unit dose strength(s)	5 mg/mL	10 mg/mL	25 mg/mL
Dosage level(s)	150 (120) mg/m^2 every 3 weeks	10 mg/kg every 3 weeks	200 mg every 3 weeks
Route of administration	IV infusion	IV infusion	IV infusion
IMP (single-arm)	IMP	IMP	IMP

Enter Arm Name (single arm)	tusamitamab ravtansine	ramucirumab	pembrolizumab
Packaging and labeling	Supplied in a 30 mL glass vial with a plastic flip-off cap, containing 125 mg/25 mL tusamitamab ravtansine, and labelled with a multilingual booklet	Supplied in a single-dose vial (100 mg/10 mL or 500 mg/50 mL) individually packaged in a carton.	Supplied in single-dose vials containing 100 mg/4 mL pembrolizumab labelled with a multilingual booklet. 1 vial per treatment box
[Current/Former name(s) or alias(es)]	None	Cyramza	Keytruda

Study medication infusion:

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

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%.

Investigational medicinal products:

Ramucirumab: Ramucirumab should be administered prior to tusamitamab ravtansine infusion. Using a controlled infusion pump, ramucirumab will be administered by IV infusion over 1 hour on D1 of each cycle. If the first infusion is tolerated, all subsequent ramucirumab infusions may be administered over 30 minutes. In case of IRR, Grade 1 or 2, the infusion rate of ramucirumab will be reduced by 50%.

Tusamitamab ravtansine: Infusion of tusamitamab ravtansine should be initiated at least 1 hour after the end of ramucirumab infusion. Using a controlled infusion pump, tusamitamab ravtansine will be administered by IV infusion over 1 hour 30 minutes. For patients with a BSA >2.20 m^2, the calculated dose of tusamitamab ravtansine will be based on a BSA of 2.20 m^2. 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. Detailed instructions for dilution and administration of the IMP is provided in Pharmacy Manual.

Pembrolizumab: Pembrolizumab will be administered after administration of tusamitamab ravtansine in the triplet cohort only. Using a controlled infusion pump, pembrolizumab will be administered as a 200 mg IV infusion over 30 minutes on Day 1 and then Q3W.

Noninvestigational medicinal products:

Premedication:

Both tusamitamab ravtansine and ramucirumab have potential risk of IRR; thus, premedication with an IV histamine-1 receptor antagonist (diphenhydramine 50 mg IV or equivalent; eg, cetirizine, promethazine, dexchlorpheniramine, according to local approval and availability) will be given approximately at least 15 minutes before ramucirumab administration. In case of IV

forms unavailability, a per os administration should be considered in an appropriate timeframe. If a participant previously experienced an IRR following a dose of ramucirumab or tusamitamab ravtansine, premedication will also include corticosteroids equivalent to 10 mg IV dexamethasone, and acetaminophen/paracetamol for future infusions. All drugs used as premedication will be entered on the concomitant premedication page.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. 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.
3. 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-IMP (NIMP; eg, deficiency in condition, appearance, pertaining documentation, labeling, expiration date) must be promptly reported to the Sponsor. Some deficiencies may be recorded through a complaint procedure (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 (except for DTP shipment, for which a courier company has been approved by the Sponsor), 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

Not applicable.

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 record precisely the date and the time of the drug administration to the participant. Deviation(s) from the prescribed dosage regimen should be recorded in the electronic case report form (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
- Dates of administration including start and end dates
- Route of administration

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

- Palliative radiotherapy may be given for control of pain (for palliative intent). If palliative radiotherapy is being considered, the Sponsor should be contacted for approval prior to initiating treatment, and prior to resuming therapy on the study.

  The irradiated area should be as small as possible and should involve no 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. The irradiated area cannot be used as a parameter for response assessment. 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.

- Prior to elective surgery, omit ramucirumab for 28 days. Resume ramucirumab no sooner than 28 days after surgery and the wound is fully healed.
- Any background therapy taken by the participant for concomitant illnesses other than cancer (eg, hormone-replacement therapy, statin, antihypertensive medication) is allowed.
- 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.

6.5.1 Treatments prohibited during the study

The following 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 (G-CSF) is not allowed during the Cycle 1 and Cycle 2 for the Part 1 of the study. Secondary prophylaxis or therapeutic administration is allowed as detailed in Section 6.6.
- Use of prophylactic erythropoietin during the first 2 cycles for the doublet cohort and during the first cycle for the triplet cohort.
- Patients treated or intended to be treated with drugs identified as CYP_{450} substrates with narrow therapeutic range (NTR) should be carefully monitored (see Appendix 9, 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 Appendix 10, Section 10.10).
- The use of contact lenses will not be permitted during the study treatment period.

Ramucirumab and pembrolizumab are not considered as a concomitant therapy and should be recorded as IMPs.

6.6 DOSE MODIFICATION

6.6.1 Doublet cohort - Part 1 (Safety Run-In)

If ≥2 of the first 3 patients or of the 6 patients treated at the initial DL present with DLTs, the SC may decide to decrease the dose of tusamitamab ravtansine to DL -1 (80 mg/m^2 in combination with 8 mg/kg ramucirumab). The tolerability of the reduced DL will be assessed in at least 6 participants. Dose reduction in the case of 2 or more DLTs for the cohort is shown in Table 9.

Table 9 - Dose reduction for doublet cohort for Part 1 (safety run-in)

Dose level (DL)	tusamitamab ravtansine	Ramucirumab
Starting dose	100 mg/m^2 Q2W	8 mg/kg Q2W
Minus -1 (DL-1)	80 mg/m^2 Q2W	8 mg/kg Q2W

BSA=body surface area; DL=dose level; Q2W=every 2 weeks.
Infusion of tusamitamab ravtansine will be administered at least 1 hour after the end of ramucirumab infusion. For patients with a BSA >2.20 m^2, the tusamitamab ravtansine dose will be calculated based on a BSA of 2.20 m^2.

6.6.2 Triplet cohort

If ≥2 of the first 3 patients or of the 6 patients treated at the initial DL present with DLTs, the SC may decide to decrease the dose of tusamitamab ravtansine to DL -1 (120 mg/m^2 in combination with 10 mg/kg ramucirumab). The tolerability of the reduced DL will be assessed in at least 6 participants. Dose reduction in the case of 2 or more DLTs for the cohort is shown in Table 10.

Table 10 - Dose reduction for triplet cohort

Dose level (DL)	tusamitamab ravtansine	ramucirumab	pembrolizumab
Starting dose	150 mg/m^2 Q3W	10 mg/kg Q3W	200 mg Q3W
Minus -1 (DL-1)	120 mg/m^2 Q3W	10 mg/kg Q3W	200 mg Q3W

DL=dose level; Q3W=every 3 weeks.
Infusion of tusamitamab ravtansine will be administered at least 1 hour after the end of ramucirumab infusion. For patients with a BSA >2.20 m^2, the tusamitamab ravtansine dose will be calculated based on a BSA of 2.20 m^2.

6.6.3 Doublet cohort (Part 1 and Part 2) and triplet cohort: Requirements for retreatment

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

- Neutrophils count ≥1.5 × 10^9/L.
- Platelets ≥100 × 10^9/L.
- Total bilirubin ≤1.5 × ULN.
- AST, ALT ≤2.5 × ULN or ≤5 × ULN in case of documented liver metastasis.
- No IMP-related toxicity Grade >1 (except for alopecia) or baseline severity.
- Urine protein:
  - <2+ on dipstick or urinalysis for C1D1,
  - ≤2+ on dipstick or urinalysis for subsequent infusions,

    OR
  - <2 g on 24 hours urine collection.
- Hypertension is controlled, every attempt should be made to control blood pressure (<140 mmHg systolic and <90 mmHg diastolic).
- Wound healing: any wound is fully healed.

6.6.4 Dose adjustment/dose delay

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.

Pembrolizumab, ramucirumab or tusamitamab ravtansine can be discontinued prematurely. The patient will remain on study treatment until the last IMP can be discontinued until disease progression, unacceptable AE, or the participant's or investigator's decision to stop the treatment. The reason for premature discontinuation will be captured in the appropriate eCRF page.

Dose modifications different from those stated in the protocol should be made only 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 (23). 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 window for tusamitamab ravtansine and ramucirumab and pembrolizumab administration is ±2 days for a Q2W (doublet cohort) and ±3 days for a Q3W administration (triplet cohort).

See Appendix 4 in Section 10.4 for further guidance in dose modification or discontinuation. Approved product label should be followed for patient receiving ramucirumab treatment for supportive care and dose modification requirement due to not listed adverse events. During the conduct of the study, second dose reduction may be needed, and need to be decided case by case discussion with the sponsor.

In case a dose reduction is necessary, the study intervention will be administered as shown in Table 11 and Table 12:

Table 11 - Dose modification for toxicity in doublet cohort

Drug name	Starting dose	1st dose reduction	2nd dose reduction
tusamitamab ravtansine	100 mg/m^2 Q2W	80 mg/m^2 Q2W	(not permitted)
ramucirumab	8 mg/kg Q2W	6 mg/kg Q2W	5 mg/kg Q2W

Table 12 - Dose modification for toxicity in triplet cohort

Drug name	Starting dose	1st dose reduction	2nd dose reduction
tusamitamab ravtansine	150 mg/m2 Q3W	120 mg/m2 Q3W	(not permitted)
ramucirumab	10 mg/kg Q3W	8 mg/kg Q3W	6 mg/kg Q3W
pembrolizumab	200 mg Q3W	(not permitted)	(not permitted)

Any patient who requires a tusamitamab ravtansine or ramucirumab dose reduction will continue to receive a reduced dose until discontinuation from tusamitamab ravtansine/ramucirumab/pembrolizumab or discontinuation from the study.

Any patient who has had 1 tusamitamab ravtansine dose reduction or 2 ramucirumab dose reductions and who experiences an event that would cause an additional dose reduction must be discontinued from tusamitamab ravtansine/ramucirumab.

If 1 of the 3 drugs (tusamitamab ravtansine or ramucirumab or pembrolizumab) is prematurely permanently discontinued, the other drug(s) can be continued until disease progression.

Retreatment of a patient requiring a dose delay of more than 1 month will need to be justified by an individual case risk-benefit assessment.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

The duration of the study for a participant will include:

- **Screening period:** up to 28 days.
- **Treatment period:** once successfully screened, enrolled participants may receive study intervention until disease progression, unacceptable AE, or the participant's or investigator's decision to stop the treatment. Each cycle of treatment will have duration of 2 weeks in doublet cohort and 3 weeks in triplet cohort. After discontinuing study intervention, participants will return to the study site approximately 30 days after the last IMP administration or before the participant receives another anti-cancer therapy, whichever is earlier, for end-of-treatment assessments.
- **Safety follow-up visit:** will be performed at 90 days after the last infusion. If ongoing related AE and all SAEs and AESI are resolved or stabilized, no further follow-up visit is needed.

For the doublet cohort, a participant who stops treatment before documented PD (achieving SD, CR or PR) should undergo a tumor assessment and an on-site follow-up visit every 12 weeks (±7 days) after the last tumor assessment until radiological disease progression, start of new anti-cancer therapy, death, the study cut-off date of the secondary ORR endpoint analysis of triplet cohort, or withdrawal of participant's consent, whichever comes first. After PD or a start of new anti-cancer therapy, a participant will be followed until any ongoing related AE/SAE is resolved or stabilized.
The study cut-off for the primary ORR endpoint analysis of doublet cohort corresponds to the date on which all evaluable treated patients have had at least 2 post baseline tumor assessments, experienced confirmed objective response, or have discontinued the study for any reason and which can be up to approximately 6 months (4 months for 2 treatment assessment, and 2 months if response confirmation is needed) from the date the last participant first administration.

The study cut-off for the secondary ORR endpoint analysis of triplet cohort corresponds to the date on which all evaluable treated patients have had at least 2 post baseline tumor assessments, experienced confirmed objective response, or have discontinued the study for any reason. This study cut-off will occur approximately 4.5 months after the date of the first IMP administration of the last participant: 3 months for 2 tumor assessments and 1.5 months if a confirmation of response is needed.

After the study cut-off dates for the primary ORR analysis of doublet cohort and for the secondary ORR analysis of triplet cohort, patients who are still receiving study treatment can continue study treatment, if clinical benefit is observed, until PD, unacceptable toxicity, or withdrawal of participant's consent, and will continue to undergo all assessments as per the study flow chart.

The expected duration of study intervention for participants may vary, based on progression date; median expected duration of study per participant is estimated as 11 months (up to 1 month for screening, a median of 6 months for treatment, and a median of 4 months for end-of-treatment assessments and safety follow-up visit).

Study Team will add details on the specific changes to follow-up for patients with ongoing treatment after final study cut-off date.

7.1 DISCONTINUATION OF STUDY INTERVENTION

7.1.1 Definitive discontinuation

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for safety and disease progression status when applicable. See Section 1.3 for data to be collected at the time of discontinuation of study intervention. All efforts should be made to document the reasons for discontinuation, and these should be recorded in the eCRF.

Ramucirumab or tusamitamab ravtansine or pembrolizumab can be discontinued prematurely. The patient will remain on study treatment until the last IMP is discontinued. The reason for premature discontinuation will be captured in the appropriate eCRF page.

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.

See the Schedule of Activities (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 PK/antigenicity 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/dosing delays

See Section 6.6.4. 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 11 [Section 10.11]).

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted. See the SOA (Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The participant will be permanently discontinued both from the study intervention and from the study at that time.

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

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

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

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

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

All study withdrawals should be recorded by the Investigator in the appropriate screens of the 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 stop participating in the study. Withdrawal of consent for intervention should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for non-participant contact follow-up, eg, medical record checks.

The site should document any case of withdrawal of consent. The patient should withdraw consent, preferably, in writing. If the patient or the patient's representative refuses or is physically

unavailable, the site should document and sign the reason for the patient's failure to withdraw consent in writing.

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

7.3 LOST TO FOLLOW UP

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

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

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

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

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SOA (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 11 (Section 10.11).
- 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 failed prescreening, limited information will be collected as detailed in Section 1.3.

During the screening period, demography, medical/surgical and disease history will be 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 extent at study entry, specific mutations including PD1 expression status and previous antitumor therapy (type, start and end dates, reason for discontinuation and response to the therapy) and smoking history.

8.1 EFFICACY ASSESSMENTS

The assessment of antitumor activity of tusamitamab ravtansine combined with ramucirumab in doublet cohort is the primary efficacy objective.

All participants treated must have at least one measurable lesion as per RECIST v1.1 for inclusion based on tumor assessment defined in the SOA, Section 1.3.

For the doublet cohort: Tumor assessment will be made every 8 weeks (±7 days window), and a scheduled assessment time point 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, initiation of further anticancer therapy, death, or study cut-off of the secondary ORR endpoint of the triplet cohort, whichever comes first; and at the end of study treatment, except if already done at last cycle. Confirmatory radiological evaluation will be performed at least 4 weeks after initial documentation of response. After IMP discontinuation, tumor assessment should be performed at EOT for patients without imaging performed within past 4 weeks, and every 12 weeks (±7 days) after the last tumor assessment until

disease progression or initiation of a new anticancer treatment, death, or the study cut-off date of the secondary ORR endpoint of the triplet cohort, whichever comes first.

For the triplet cohort: Tumor assessment will be made every 6 weeks (±7 days window), and a scheduled assessment time point 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 6 weeks during the study treatment period until IMP discontinuation; and at the end of study treatment, except if already done at last cycle. Confirmatory radiological evaluation will be performed at least 4 weeks after initial documentation of response. After IMP discontinuation, tumor assessment should be performed at EOT for patients without imaging performed within past 4 weeks.

For both cohorts: Brain CT-scan or MRI should be performed at baseline and followed only for patients with brain lesions at baseline. Imaging assessments during the on-treatment period are to be scheduled using the Cycle 1, Day 1 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. Delay of an imaging assessment to conform to treatment delay is not permitted. The same tumor assessment technique must be used throughout the study for a given lesion/participant.

For the doublet cohort, secondary efficacy endpoints will include DOR, PFS, and DCR.

The RECIST v1.1 criteria will be followed for assessment of tumor response; see Appendix 7 for details (Section 10.7).

8.2 SAFETY ASSESSMENTS

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

8.2.1 Physical examinations

- A complete physical examination will include, at a minimum, temperature, blood pressure, heart rate (see vital signs in Section 8.2.3), and assessments of the major body systems, including cardiovascular and central nervous systems. Weight will also be measured and recorded before premedication and IMP administration at all treatment visits, and at the End of treatment and follow-up visits. Height will be recorded only at Screening.
- 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 AE.

8.2.2 Specific ocular tests

Specific complete ocular tests at baseline will include: 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, etc) at each visit before each study intervention. Start and end dates of symptoms will be collected.
- 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 (eg, blurred vision, photophobia), complete ocular tests will be repeated at the time of the occurrence of the ocular toxicity, if any regardless of the grade. Thereafter, 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.

8.2.3 Vital signs

- Temperature, blood pressure, heart rate will be assessed during each physical examination (Section 8.2.1).
- For blood pressure assessments, manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).

8.2.4 Cardiac assessment

8.2.4.1 Electrocardiograms

- A single 12-lead ECG is required at baseline screening; before starting and after completing the first IMP administration (within 30 minutes after the end of the infusion); before IMP administration at each cycle; and at the end of treatment evaluation (between Day 22 and Day 30 after the last IMP administration). This test can be performed on the same day before the study intervention administration, or on the day before. An ECG is to be repeated as clinically indicated.
- A single 12-lead ECG will be obtained using an ECG machine that automatically calculates the heart rate and measures PR, QRS, and QT intervals.

- ECGs will be interpreted by a qualified physician at the site as soon after the time of ECG collection as possible, and ideally while the patient is still present, should additional ECGs be performed or for immediate patient management should any clinically relevant findings be identified.

8.2.4.2 Echocardiogram or MUGA scan

An echocardiogram or multigated acquisition (MUGA) scan to evaluate left ventricular ejection fraction (LVEF) will be evaluated during screening period, and whenever clinically indicated.

8.2.5 Clinical safety laboratory assessments

See Appendix 2 (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. In general, these tests will be done at each cycle; during the first 2 cycles, hematology and liver function tests will be assessed weekly.

If Grade 4 neutropenia occurs, assess ANC every 2 to 3 days until ANC $\geq 0.5 \times 10^9$/L.

In case of Grade ≥3 abnormal liver function tests, additional tests will be done every 2 to 3 days until recovery to the baseline value. Additional tests will be performed when clinically appropriate. This test can be performed before the study intervention administration on the same day or the day before.

The Investigator must review the laboratory reports and must document this review in the source documents.

8.2.6 Guidelines for management of adverse events

Management of the AE related to tusamitamab ravtansine and ramucirumab and pembrolizumab is summarized in Appendix 4 (Section 10.4); for specific AE related to ramucirumab or pembrolizumab intake, please refer to the current prescribing information leaflet; the most relevant reported events are summarized in this section as reminder.

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 in Appendix 4 (Section 10.4).

As with other monoclonal antibodies, IRRs may occur during or following ramucirumab or tusamitamab ravtansine or pembrolizumab administration. Patients should be closely monitored for signs and symptoms indicative of an IRR from the initiation of the infusion in an area where resuscitation equipment and other agents (such as epinephrine and corticosteroids) are readily available.

A 1-hour observation period following the ramucirumab infusion is mandatory for the first 2 infusions. If the patient shows no evidence of an IRR with the first 2 infusions of ramucirumab, no observation period is required for subsequent infusions. In the event an IRR occurs thereafter, the 1-hour observation should be reinstituted. Symptoms of IRRs include rigors/tremors, back pain/spasms, chest pain and/or tightness, chills, flushing, dyspnea, wheezing, hypoxia, and paresthesia. In severe cases, symptoms include bronchospasm, supraventricular tachycardia, and hypotension. If the patient experiences a Grade 2 IRR, interrupt the infusion and treat the patient with anti-allergic medication. If symptoms resolve, resume the infusion at a reduced rate (50%).

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), as required during the treatment (ie, on occurrence of ocular symptoms such as blurred vision, photophobia, pain), at the EOT visit, and when relevant at follow-up 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, unless less frequent assessment is recommended by an ophthalmologist, until resolution to Grade 1. Subsequently, the participant 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 an ophthalmologist when applicable.

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 an 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 other than prevention of dry eye with artificial tears and/or hyaluronic ophthalmic gel is recommended; the use of contact lenses is not permitted during the treatment period. Corticosteroid-containing ocular drugs are recommended for the management of keratopathy/keratitis in the case that ocular symptoms occur, and treatment will be performed based on discretion of ophthalmologist. Dose modification and recommendations are further described in Appendix 4 (Section 10.4).

After resuming study treatment, a patient who had Grade ≥2 keratopathy/keratitis should be followed with standard ocular exams (ie, slit lamp examination under dilatation and visual acuity) every 2 cycles, even if symptoms are no longer reported. If no event recurs during the next 4 cycles, then regular follow-up (ie, symptom assessment at each visit with standard ocular exam in case of any ocular sign/symptom) is applied.

8.2.6.3 Management of anemia

Close surveillance of any signs and symptoms is required: a routine blood hematology workup, including red blood cell (RBC) counts, hemoglobin, hematocrit, WBC with differential, and platelet counts will be done weekly during the first 2 cycles, and thereafter each treatment cycle before IMP administration. Patients should not start Cycle 1 treatment if hemoglobin is <9.0 g/dL. To be eligible for the study and to receive the first study treatment, the participant must have been transfusion-free for 2 weeks. During the treatment period, erythrocyte transfusion can be given, upon Investigator decision. Erythropoietin can be given at the discretion of the Investigator, except during Screening and the first 2 cycles. Cycle delays or modifications should be compliant with Appendix 4 (Section 10.4).

8.2.6.4 Management of neutropenia

In patients who experienced either Grade 3 or 4 febrile neutropenia or Grade 4 decreased neutrophil count (<500 cells/mm^3) for more than 1 week during study intervention, prophylactic G-CSF should be implemented per ASCO guidelines (23) to ensure dose intensity (Appendix 4 in Section 10.4). Doses of tusamitamab ravtansine should be reduced in case of recurrent events even after prophylactic G-CSF use.

If the patient continues to experience these reactions at a lowered dose, the treatment should be discontinued (Section 7).

8.2.6.5 Liver function tests

Hepatic enzyme increase has been reported with tusamitamab ravtansine administration as monotherapy or ramucirumab. Patients should be carefully followed and in case of Grade ≥3 abnormal liver function tests, additional liver function tests will be done every 2 to 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 ramucirumab administration, the current product leaflet should be followed.

Grade ≥3 (ie, >5 × ULN) increased liver enzyme events should be reported as AESIs.

8.2.6.6 Hypertension

An increased incidence of severe hypertension (CTCAE Grade 3) has been reported in patients receiving ramucirumab as compared with placebo. In most cases, hypertension was controlled using standard antihypertensive treatment. Preexisting hypertension should be controlled before starting ramucirumab treatment. Monitoring of blood pressure is required during ramucirumab therapy. Every attempt should be made to control blood pressure to systolic <140 mmHg and diastolic <90 mmHg prior to starting treatment with ramucirumab. Routine clinical and laboratory monitoring is required in patients who again develop hypertension or experience a deterioration in previous hypertension.

Withhold ramucirumab for severe hypertension until medically controlled. Permanently discontinue ramucirumab for medically significant hypertension that cannot be controlled with antihypertensive therapy or in patients with hypertensive crisis or hypertensive encephalopathy.

8.2.6.7 Proteinuria

Proteinuria is an adverse effect for all therapies targeting the vascular endothelial growth factor (VEGF)/VEGFR-2 pathway, including ramucirumab. Proteinuria has been associated with ramucirumab in clinical studies; the majority of events were Grade 1 or 2.

Monitor proteinuria by urine dipstick and/or urinary protein creatinine ratio. If the result of the urine dipstick is 2+ or greater, perform a 24 hours urine collection for protein measurement.

Withhold ramucirumab for urine protein levels of 2 or more grams collected over 24 hours. Reinitiate ramucirumab at a reduced dose once the urine protein level returns to less than 2 grams over 24 hours. Permanently discontinue ramucirumab for urine protein levels greater than 3 grams over 24 hours, or in the setting of nephrotic syndrome.

8.2.6.8 Bleeding/Hemorrhage

Ramucirumab is an antiangiogenic therapy and has the potential to increase the risk of severe bleeding. Permanently discontinue ramucirumab in patients who experience severe (Grade 3 or Grade 4) bleeding.

8.2.6.9 Arterial Thromboembolic Events

Serious, sometimes fatal, arterial thromboembolic events (ATEs), including myocardial infarction, cardiac arrest, cerebrovascular accident, and cerebral ischemia, occurred across clinical trials. Permanently discontinue ramucirumab in patients who experience an ATE.

8.2.6.10 Peripheral neuropathy

Participants with a known history of peripheral neuropathies and/or patients having received medications known to cause peripheral neuropathies (eg, prior antitubulin, platinum and/or taxanes) are at high risk of developing neuropathy. Peripheral neuropathies potentially present as signs and symptoms of sensory (paresthesia, dysesthesias, pain, and change in proprioception), motor (weakness), and neural dysfunctions.

There is no further recommendation beyond routine guidance on prevention and treatment of peripheral neuropathy. Cycle delays or modifications should be compliant with Appendix 4 (Section 10.4).

8.2.6.11 Colitis (including hemorrhagic)

In study TED13751 evaluating tusamitamab ravtansine in patients with several cancer types, a limited number of participants developed colitis. Based on clinical observations, patients with known underlying colitis or gastrointestinal tract conditions are noted to be at highest risk for such events. The monitoring of patients for GI toxicities will rely on careful evaluation by routine history, physical examination, and standard laboratory examination. Close surveillance of any signs and symptoms is required, with additional routine hematology workup (hemoglobin, hematocrit, and WBC with differential and platelet counts) whenever indicated. As 1 case of Grade 4 erosive colitis has been reported, it is recommended to conduct close surveillance of any diarrhea event, with further exams when clinically indicated. Treatment is per patient condition, based on Investigator discretion.

8.2.7 Immune-related adverse reactions

Immune-related adverse reactions are provided in Appendix 4 (Section 10.4).

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 Adverse events, treatment-emergent adverse events, and adverse events of special interest

The safety profile of the IMP will be based on incidence, severity (as graded by the NCI CTCAE V5.0), and cumulative nature of TEAEs. TEAEs are defined as AEs that develop, worsen or become serious during the on-treatment period. For this study, the on-treatment period will be defined as the period from the time of first dose of IMP to at least Day 30 of the last tusamitamab ravtansine administration. Each patient will be assessed preferably by the same physician for AEs and according to the NCI CTCAE V5.0 classification.

An AESI is an AE (serious or nonserious) 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
- 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 or unit per weight.
- All protocol-defined DLT (Section 4.1).

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

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

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

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 30 days after the last study intervention administration.

All AEs 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 30 days 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. 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 the conclusion of 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 the follow-up period, SAEs (regardless of relationship to IMP) ongoing at the end of study treatment and IMP-related AEs ongoing at the end of study treatment, as well as new IMP-related AE/SAEs, 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 nonserious AESIs (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 7.3). 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 (SUSARs) 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 (IB for tusamitamab ravtansine and SPC for ramucirumab).
- 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 3 (Section 10.3).
- 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 after the last IMP administration. All death that occurs within 30 days of the 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.

In case of progression of the underlying disease, with no radiologic documentation, symptoms leading to disease progression should be reported as an AE.

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 form within required timelines.

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

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 eCRF.

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

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

8.5.1 Non-compartmental analysis

Pharmacokinetic parameters of tusamitamab ravtansine will be calculated using non-compartmental methods from concentrations assayed in Part 1 (safety run-in). The parameters will include, but may not be limited to, those listed in Table 13:

Table 13 - List of pharmacokinetic parameters and definitions

Parameters	Definition
C_{eoi}	Concentration observed at the end of IV infusion
C_{max}	Maximum concentration observed after infusion
t_{max}	Time to reach C_{max}
C_{last}	Last concentration observed above the lower limit of quantification after infusion
t_{last}	Time of C_{last}
C_{trough}	Concentration observed just before treatment administration during repeated dosing
$AUC_{0\text{-}14d}$	Area under the plasma concentration versus time curve calculated using the trapezoidal method from time 0 to 14 days.

Ramucirumab C_{trough} values for Part 1 and Part 2 will be reported.

8.5.2 Population approach

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

8.6 PHARMACODYNAMICS

Approximately 3 mL venous blood samples for measurement of circulating CEA will be collected at prescreening, at baseline, and during the treatment period as close as possible to tumor assessments.

For CEA sample collection scheduled on the day of a treatment visit, samples should be drawn prior to initiation of ramucirumab infusion and tusamitamab ravtansine infusion.

8.7 GENETICS

Genetics are not evaluated in this study.

8.8 BIOMARKERS

Collection of samples for other biomarker research is also part of this study. The following samples for biomarker research are required and will be collected from all participants in this study as specified in the SoA:

- Tumor tissue samples will be collected and assayed for CEACAM5 expression to determine eligibility for this study.
- Blood samples will be collected for IgG measurement to explore the impact of IgG level on PK of tusamitamab ravtansine.

The level of IgG in blood drawn pre-infusion on Day 1 of Cycle 1 will be determined by a central laboratory. For this test, 2 mL of blood, corresponding to 1 mL of serum, will be collected. Instructions for the collection and handling of biological samples will be provided by the Sponsor in a separate laboratory manual. Samples may be stored for a maximum of 15 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the Sponsor to enable further analysis of biomarker responses to tusamitamab ravtansine.

8.9 IMMUNOGENICITY ASSESSMENTS

Blood samples will be collected for assessing the presence of ATA against tusamitamab ravtansine in plasma from all participants as described in the PK/ATA flowcharts (see Section 1.3.3). These samples will be tested by the Sponsor's designee.

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

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

8.10 HEALTH ECONOMICS

Not applicable.

8.11 USE OF BIOLOGICAL SAMPLES AND DATA FOR FUTURE RESEARCH

Future research may help further the understanding of disease subtypes, disease biology, related conditions, drug response, and toxicity, and can help identify new drug targets or biomarkers that predict a patient's response to treatment. Therefore, when participants provide written consent (Appendix 1, Section 10.1.3), data and biological samples will be stored and used for future research unless prohibited by local laws or IRBs/IECs (in such a case, consent for future use of samples will not be included in the local ICF).

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

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

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

All study participant data and samples will be coded such that no participant direct identifiers will be linked to them. Coded data and samples may be transferred to a Sponsor site (or a subcontractor site), which may be located outside of the country where the study is conducted. The Sponsor adopts safeguards for protecting participant confidentiality and personal data (Section 10.1.4).

Samples will be stored for a maximum of 15 years after the end of the study. Any samples remaining at the end of retention period will be destroyed. If a participant requests destruction of his/her samples before the end of the retention period, the Investigator must notify the Sponsor (or its contract organization) in writing. In such a case, samples will be destroyed and related coded data will be anonymized unless otherwise required by applicable laws.

Study participants' coded data will be stored for future research for up to 25 years after the end of the study. If data are still considered of important scientific value after this period, coded data already available will be anonymized unless otherwise required by applicable laws (the same will apply to the data of a study participant who has requested the destruction of his/her samples).

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

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

The doublet cohort contains 2 parts:

Part 1 (safety run-in) aims to establish the recommended dose (RD) of tusamitamab ravtansine in combination with ramucirumab according to DLTs observed.

Part 2 is designed to obtain preliminary efficacy, safety, and PK data on tusamitamab ravtansine administered in combination with ramucirumab to participants with NSQ NSCLC. As the second part is not intended to explicitly test a hypothesis, calculations of power and Type I error were not considered in the study design.

The triplet cohort (safety run-in only) is designed to assess the tolerability and to confirm the recommended dose of tusamitamab ravtansine in combination with ramucirumab and pembrolizumab in the NSQ NSCLC population.

9.2 SAMPLE SIZE DETERMINATION

In the doublet cohort, assuming a prescreening failure rate of 80% and a study screening failure rate of 20%, approximately 225 participants will be prescreened to achieve a total of up to approximately 36 treated participants, including Part 1 (safety run-in) and Part 2.

In the triplet cohort, assuming a prescreening failure rate of 79% and a study screening failure rate of 23% based on the doublet cohort, approximately 74 participants will be prescreened to achieve a total of up to approximately 12 DLT evaluable participants.

9.2.1 Sample size for the doublet cohort, safety run-in (Part 1)

The actual sample size is expected to vary depending on DLTs observed. It is anticipated that around 6 to 12 DLT-evaluable participants will be enrolled in the safety run-in part of the cohort.

9.2.2 Sample size for the doublet cohort, Part 2

The initial plan is to treat a total of 30 participants evaluable (at least one post-baseline tumor assessment) for activity. The 6 participants treated at the recommended dose level in the safety run-in part will also be evaluable for this second part of the cohort.

Estimated ORR and 95% exact CI by numbers of responders from a sample size of 30 participants evaluable for activity are summarized in Table 14.

Table 14 - Estimated objective response rate (ORR) depending on number of responders

Number of Responders (N=30)	Objective Response Rate in % (95% Clopper-Pearson CI)
6	20.00% (7.71% - 38.57%)
8	26.67% (12.28% - 45.89%)
9	30.00% (14.73% - 49.40%)
11	36.67% (19.93% - 56.14%)
12	40.00% (22.66% - 59.40%)

CI=confidence interval.

9.2.3 Sample size for the triplet cohort (safety run-in only)

The actual sample size is expected to vary depending on DLTs observed. It is anticipated that around 6 to 12 DLT evaluable participants will be enrolled in the safety run-in of the triplet cohort.

9.3 POPULATIONS FOR ANALYSES

For purposes of analysis, the following populations are defined (Table 15):

Table 15 - Populations for analyses

Population	Description
Pre-screened	All participants who signed the prescreening informed consent for CEACAM5 assay assessment of their biopsy.
Screened	All participants who signed informed consent for study participation
All-treated	All registered participants exposed to the study treatment, regardless of the amount of treatment administered. This population is the primary population for analysis of all efficacy parameters.
DLT-Evaluable	For the doublet cohort: Participants who received 2 cycles with at least 80% of the intended dose for both tusamitamab ravtansine and ramucirumab at each of the two first infusions unless they discontinued the study intervention before the end of Cycle 2 due to a DLT. For the triplet cohort: Participants who received 1 cycle with at least 80% of the intended dose for each IMP of the combination. Participants should have completed Cycle 1 unless they experienced a DLT before the end of Cycle 1.
Activity (applicable for doublet cohort only)	All treated participants who have measurable disease at study entry and at least 1 post-baseline evaluable tumor assessment. Participants with an early clinical progression or an early death due to disease progression (ie, before first planned tumor assessment) will also be included in this set. This population is the secondary population for analysis of efficacy parameters of the doublet cohort.
PK	All participants from the all-treated population who have actually received at least 1 dose or a part of a dose of tasumitamab ravtansine (SAR408701) or ramucirumab with at least 1 evaluable post-baseline concentration.
ATA	All treated participants with at least 1 post-baseline ATA result (negative, positive, or inconclusive).

9.4 STATISTICAL ANALYSES

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

The statistical analyses of the doublet and triplet cohorts will be presented separately.

9.4.1 Efficacy analyses

All efficacy analyses will be performed on the all-treated population (primary population for analysis of all efficacy parameters). In addition, the primary endpoint (ORR) for the doublet cohort will be analyzed on the Activity population (secondary population). All efficacy analyses will be summarized only for the subgroup of participants treated at the recommended dose (ie, excluding participants treated at the starting dose if this differs from the RP2D).

Objective response rate, as well as PFS, DOR, and DCR will be derived using the local radiologist's/Investigator's assessment. A summary of efficacy analyses is provided in Table 16.

Table 16 - Efficacy analyses

Endpoint	Statistical Analysis Methods
Primary for doublet cohort / Secondary for triplet cohort	
• ORR	Descriptive statistics and 95% CIs using the Clopper-Pearson method.
Secondary for doublet cohort	
• DOR	Kaplan-Meier method for descriptive statistics. Median DOR and 95% CI will be provided.
• PFS	Kaplan-Meier method for probabilities of being event free at different time points. Median PFS and 95% CI will be provided.
• DCR	Descriptive statistics and 95% CIs using the Clopper-Pearson method.
Tertiary/exploratory	
Circulating CEA at prescreening, screening, and during the treatment period	Will be described in the SAP.

ORR=objective response rate; DCR=disease control rate; DOR=duration of response; PFS=progression free survival; CI=confidence interval.

9.4.1.1 Analysis of primary efficacy endpoint for the doublet cohort / Secondary efficacy endpoint for the triplet cohort

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

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

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

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

9.4.1.2 Analysis of secondary efficacy endpoints for the doublet cohort

The 3 secondary efficacy endpoints are DOR, PFS, and DCR for the doublet cohort.

9.4.1.2.1 Duration of response

Duration of response will be summarized only for the subgroup of participants who have achieved confirmed objective response in the all-treated population.

The definition of DOR is the time from the date of first initial occurrence of the confirmed CR or PR to the date of first documentation of objective PD according to RECIST v1.1 before the initiation of any post-treatment anti-cancer therapy or death due to any cause.

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

9.4.1.2.2 Progression-free survival

Progression-free survival is defined as the time from the date of first administration of IMP to the date of the first documentation of objective PD according to RECIST v1.1 or death due to any cause, whichever occurs first.

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

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

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

9.4.1.2.3 Disease control rate

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

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

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

9.4.2 Safety analyses

All safety analyses will be performed on the all-treated population for the Part 1 (safety run-in part) and Part 2 of the doublet cohort, and for the triplet cohort, by dose level and overall. Summary of Safety data will be performed by participant. For each safety parameter, a baseline value will be defined as the last value or measurement taken up to the first administration of the IMP.

A summary of safety analyses is provided in Table 17.

Table 17 - Safety analyses

Endpoint	Statistical Analysis Methods
Primary	
For the doublet cohort: Incidence of study drug-related dose-limiting toxicity (DLTs) at Cycle 1 and Cycle 2 For the triplet cohort: Incidence of study drug-related DLTs at Cycle 1	Descriptive statistics
Secondary	
Incidence of TEAEs and SAEs and laboratory abnormalities according to NCI CTCAE V5.	Descriptive statistics
Incidence of ATAs against tusamitamab ravtansine (SAR408701)	Will be described in the SAP
Exploratory	No exploratory endpoint is defined for safety analyses.

ATA=anti-therapeutic antibodies; TEAE=treatment emergent 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 or provide an addendum to informed consent (for participants who already have available CEACAM5 expression result) to the day before the screening informed consent.
- The screening period is defined as the time from when the participants give screening informed consent to the first administration of the IMP.

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

9.4.2.1 Analysis of primary safety endpoint

Dose-limiting toxicities observed during the DLT observation period (Cycle 1 and Cycle 2 for the doublet cohort; Cycle 1 for the triplet cohort) will be summarized on the DLT-evaluable population, by dose level. In addition, AEs that meet the DLT criteria in subsequent cycles will be summarized on the all-treated population. Details will be provided by patient.

9.4.2.2 Analysis of adverse events

Adverse events will be collected from the time prescreening informed consent is signed until at least 30 days after the last infusion of the study treatment. All AEs will be categorized according to NCI-CTCAE V5.0 and classified by system organ class (SOC)/ preferred term (PT) according to the latest available version of the MedDRA dictionary.

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

The NCI-CTCAE grade will be taken into account in the summary. 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. Pre-screening, screening and post-treatment AEs will be described separately.

Treatment-emergent adverse events:

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

- TEAEs
- Grade ≥3 TEAEs
- Grade 5 TEAEs (any TEAE with a fatal outcome during the treatment period)
- Serious TEAEs
- TEAEs leading to definitive treatment discontinuation
- Treatment-related TEAEs
- Treatment-related 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 all-treated population. Similar summaries will be prepared for treatment-related TEAEs, TEAEs leading to definitive discontinuation, TEAEs leading to dose modification, serious TEAEs, TEAEs with fatal outcome, AESIs, and AEs/SAEs occurring during the post-treatment period. In addition, the number (%) of participants with any Grade 5 AE (TEAE and post-treatment) will be summarized.

9.4.2.3 Analysis of deaths

The following deaths summaries will be generated:

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

9.4.2.4 Analysis 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 clinical chemistry results will be graded according to the NCI-CTCAE V5.0, when applicable. Number and percentage of participants with laboratory abnormalities (all grades and by grade) using the worst grade during the treatment period will be provided for the all-treated population.

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.

9.4.2.5 Analysis of immunogenicity

Immunogenicity analyses and the potential impact on PK, safety and efficacy will be described in the SAP, and will be performed on the ATA population.

9.4.3 Other analyses

Analyses of PK and pharmacodynamics and exploratory biomarker analyses will be described in the statistical analysis plan, to be finalized before database lock.

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

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 11 (Section 10.11).

9.5 INTERIM ANALYSES

No interim analysis is planned.

9.6 DATA MONITORING COMMITTEE (DMC)

Not applicable.

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 or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative 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. However, if the reason for the temporary screen failure is a reason that might have altered the participant's initial given agreement to participate, the Investigator should ask the participant to confirm willingness to continue or repeat some screening procedures and to participate in the trial. This oral agreement should be documented in the participant's chart. Participants who screen failed and then rescreen need to re-sign a new screening ICF.
- A participant who has CEACAM5 results available from a prior study must sign an addendum to the informed consent; no additional prescreening informed consent will be required.
- For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 11 (Section 10.11).

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 African-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 Committee Structure

Study committee

The SC includes the Investigators or designees and Sponsor team members and, when appropriate, *ad hoc* experts. Decisions to continue the enrollment at a dose level or to reduce the dose to be tested will be made after the appropriate data are collected and reviewed by the SC. The SC will convene regularly (eg, every 2 weeks) during Part 1 of the study (run-in) in the doublet cohort and during the triplet cohort DLT evaluation period; and may meet *ad hoc* for specific discussions. Meeting minutes will be documented.

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, EU clinicaltrialregister (eu.ctr), and sanofi.com, as well as some national registries.

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

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: clinicalstudydatarequest.com.

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 eCRF must have a source document. The Investigator/delegated site staff will report all the original data in the participant's medical chart or in a study-specific source document created by him/her. If such a document is used, the template should be reviewed by the CRA. A list of source documents and their locations 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 study termination by the Sponsor, as well as reasons for the early closure of a study site by the Sponsor or Investigator may include, but are not limited to:

- For study termination:
  - Information on the product leads to doubt as to the benefit/risk ratio
  - Discontinuation of further study intervention development
- For site termination:
  - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
  - Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator
  - Total number of participants included earlier than expected

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 18 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, at End of treatment visit, and the 3 month follow-up, as detailed in the SOA (Section 1.3). Women of child-bearing potential must have a negative serum pregnancy test result within 7 days prior to the initial intervention; at the End of treatment evaluation (30 ±5 days after the last IMP administration); and at the Follow-up (90 ±7 days after the last IMP administration). Additionally, during the treatment period, serum/urine pregnancy tests will be performed at the beginning of the visit every 4 weeks (ie, every 2 cycles/every other cycle).

Table 18 - Protocol-required safety laboratory assessments

Laboratory assessments	Parameters
Hematology	
	Platelet count
	Red blood cell (RBC) count
	Hemoglobin
	Hematocrit
	White blood cell (WBC) count with differential:
	Neutrophils
	Lymphocytes
	Monocytes
	Eosinophils
	Basophils
Clinical blood chemistry[a]	
	Urea/blood urea nitrogen (BUN)
	Creatinine
	Glucose
	Potassium
	Sodium
	Calcium
	Aspartate aminotransferase (AST)/ Serum glutamic-oxaloacetic transaminase (SGOT)
	Alanine aminotransferase (ALT)/ Serum glutamic-pyruvic transaminase (SGPT)
	Alkaline phosphatase
	Total and conjugated bilirubin
	Total protein
	Albumin
	LDH
	Coagulation parameters (INR, aPTT)
Thyroid function (triplet cohort only)	Thyroid-stimulating hormone (TSH)
	Total tri-iodothyronine (T3)
	Free thyroxine (FT4)
Serum/urine pregnancy[b]	

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 4 AST/ALT increase must be reported as an SAE. Investigators must document their review of each laboratory safety report.

b Only for WOCBP.

10.3 APPENDIX 3: ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

10.3.1 Definition of AE

AE definition

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

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

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease), eg:
  - Leading to IMP discontinuation or modification of dosing, and/or
  - Fulfilling a seriousness criterion, and/or
  - Defined as an AESI.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- “Lack of efficacy” or “failure of expected pharmacological action” per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. Also, “lack of efficacy” or “failure of expected pharmacological action” also constitutes an AE or SAE.

Events NOT meeting the AE definition

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

10.3.2 Definition of SAE

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.

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

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to the Monitoring Team in lieu of completion of the Sanofi/AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the 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 NCI CTCAE v.5.0 categories: Mild; Moderate; Severe.

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 that a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the 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 the 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 the 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.

10.3.4 Reporting of SAEs

SAE reporting to Sanofi via an electronic data collection tool

- The primary mechanism for reporting an SAE to the 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 the 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 the Investigator Study File.

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

Event	Symptoms severity (Nadir) (NCI CTCAE v5)	Management of IMP dosing (ramucirumab))	Management of IMP dosing (tusamitamab ravtansine)	Supportive care guidelines
Infusion-related reaction	Grade 1-2 Mild-moderate Eg, Grade ≤2 nausea, headache, tachycardia, hypotension, rash, shortness of breath.	Interrupt ramucirumab infusion and start appropriate treatment. Reduce infusion rate by 50%	Interrupt tusamitamab ravtansine infusion. tusamitamab ravtansine may be resumed only after patient recovery, at half the previous infusion rate[a].	Give diphenhydramine 50 mg IV and/or dexamethasone 10 mg IV. ramucirumab label should be followed Dexamethasone can be added as premedication for upcoming cycles for tusamitamab ravtansine
	Grade 3-4 Severe Eg, symptomatic bronchospasm, urticaria lesions covering >30% BSA, hypotension, angioedema.	Interrupt ramucirumab infusion and prematurely definitively discontinue ramucirumab	Interrupt tusamitamab ravtansine infusion and prematurely discontinue tusamitamab ravtansine and consider infusion delay.	Give diphenhydramine 50 mg IV and/or dexamethasone 10 mg IV and/or epinephrine and any required treatment per investigator judgement.
Ocular toxicity: Keratopathy/keratitis[b] associated with tusamitamab ravtansine	Grade 1 - Asymptomatic Corneal lesions only observed on routine ocular examination and not requiring topical treatment.	Administer ramucirumab at same dose, and same day as tusamitamab ravtansine	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).	Standard ocular examination is planned as recommended by the ophthalmologist.
	Grade 2 Symptomatic or requiring topical treatment (curative) or limiting instrumental activity of daily life. Moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline)	Administer ramucirumab as planned, and re-introduce tusamitamab ravtansine when recovery to Grade 1	1st episode: Omit tusamitamab ravtansine until resolution to Grade 1 (asymptomatic) and restart tusamitamab ravtansine at the same dose. 2nd episode: Omit SAR until resolution to Grade 1 (asymptomatic) and tusamitamab ravtansine dose reduction. 3rd episode: depending on benefit risk, premature definitive discontinuation of tusamitamab ravtansine may be envisaged	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, Management of study drug upon recurrence to be discussed according to Grade of the event at recurrence, clinical benefit from study drug and recommendation from the ophthalmologist.

Event	Symptoms severity (Nadir) (NCI CTCAE v5)	Management of IMP dosing (ramucirumab))	Management of IMP dosing (tusamitamab ravtansine)	Supportive care guidelines
	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 selfcare activity of daily life	Administer ramucirumab as planned, and re-introduce tusamitamab ravtansine when recovery to Grade 1	1st episode: Omit tusamitamab ravtansine until resolution (asymptomatic) and restart tusamitamab ravtansine with dose reduction. 2nd episode: definitive discontinuation of tusamitamab ravtansine.	Standard ocular examination weekly until resolution[c, d,] Start curative treatment per ophthalmologist recommendation. After resuming study treatment, participant should be followed with standard ocular examination by every 2 cycles, even asymptomatic during next four cycles. If no recurrence, standard process with follow-up with ocular symptom is resumed Management of study drug 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 or best corrected visual acuity of 20/200 or worse in the affected eye.	Administer ramucirumab as planned,	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.
Conduction disorder associated with tusamitamab ravtansine	Grade 1 Mild symptoms	Administer ramucirumab as planned,	tusamitamab ravtansine administration to be continued upon decision by the Investigator and Sponsor, depending on the nature of the conduction disorder.	ECG performed once weekly until event resolution. Additional evaluations such as LVEF and Holter monitoring should be performed when relevant.
	Grade ≥2	Administer ramucirumab as planned,	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.

Event	Symptoms severity (Nadir) (NCI CTCAE v5)	Management of IMP dosing (ramucirumab))	Management of IMP dosing (tusamitamab ravtansine)	Supportive care guidelines
Peripheral neuropathy	Grade 1: Asymptomatic	Administer ramucirumab as planned,	Administer tusamitamab ravtansine as planned,	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 until recovery to ≤ Grade 1; at next cycle, administer ramucirumab as planned,	Delay cycle until recovery to ≤ Grade 1 and dose reduction if no improvement with dose delay	
	Grade 3: Severe symptoms; limiting self care Activities of Daily Living	Administer ramucirumab as planned,	Definitive discontinuation of tusamitamab ravtansine	
	Grade 4: Life-threatening consequences; urgent intervention indicated	Administer ramucirumab as planned,	Definitive discontinuation of tusamitamab ravtansine	
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 until recovery of absolute neutrophil count >1500/mm^3. Restart when absolute neutrophil count >1500/mm^3 at the same dose. Prophylactic G-CSF should be considered in all subsequent cycles	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 cycles	Follow ASCO guidelines on usage G-CSF and antibiotherapy (20, 23). Repeat test every 3 days.
	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 with ramucirumab at the same dose and administer growth factors 2nd episode: administer ramucirumab as the same dose 3rd episode: definitive discontinuation of IMPs	Delay the cycle until absolute neutrophil count >1500/mm^3. 1st episode administer tusamitamab ravtansine next cycle at the same dose and administer growth factors 2nd episode: administer tusamitamab ravtansine at reduced dose 3rd episode: definitive discontinuation	Follow ASCO guidelines onG-CSF usage and antibiotherapy. Repeat test every 3 days.

Event	Symptoms severity (Nadir) (NCI CTCAE v5)	Management of IMP dosing (ramucirumab))	Management of IMP dosing (tusamitamab ravtansine)	Supportive care guidelines
Febrile neutropenia	Grade 3 Absolute neutrophil count <1000/mm^3 with a single temperature of >38.3ºC (101ºF) or a sustained temperature of ≥38ºC (100.4ºF) for more than 1 hour	Delay cycle until absolute neutrophil count >1500/mm^3. 1st episode administer next cycle at the same dose and administer G-CSF 2nd episode: administer ramucirumab 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 tusamitamab ravtansine at reduce dose 3rd episode: definitive discontinuation	To ensure relative dose intensity, 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 (23)
	Grade 4 Life-threatening consequences	Administration changes to be decided at the Investigator's discretion per product label	Administration changes to be decided at the Investigator's discretion. 1st episode: administer next cycle at reduced dose and administer G-CSF 2nd episode: definitive discontinuation	
Hypertension	Grade 3 Severe hypertension	Withhold ramucirumab until controlled with medical management, and restart at same dose	Administer tusamitamab ravtansine as planned	
	Grade 4 Severe hypertension that cannot be controlled with antihypertensive therapy	Definitively discontinue ramucirumab	Administer tusamitamab ravtansine as planned	
Proteinuria	First occurrence of increased urine protein levels greater than or equal to 2 g per 24 hours	Omit ramucirumab until urine protein level is ≤2 g per 24 hours; then resume ramucirumab at a reduced dose (in doublet cohort, 8 mg at 1st episode, then 5 mg if 2nd episode and in triplet cohort,8 mg at 1st episode, then 6 mg if 2d episode)	Administer tusamitamab ravtansine as planned	
	Reoccurrence of urine protein level greater than 2 g per 24 hours following initial dose reduction	Omit ramucirumab until protein level is ≤2 g per 24 hours; then resume ramucirumab at a reduced dose:(6 mg or 5 mg)	Administer tusamitamab ravtansine as planned	
	Urine protein level greater than 3 g per 24 hours or in the setting of nephrotic syndrome	Definitvely discontinue ramucirumab	Consider benefit/risk for the patient to continue or delay tusamitamab ravtansine infusion	

Event	Symptoms severity (Nadir) (NCI CTCAE v5)	Management of IMP dosing (ramucirumab))	Management of IMP dosing (tusamitamab ravtansine)	Supportive care guidelines
Hemorrhage	Grade 3 or 4	Definitively discontinue ramucirumab	Permanently discontinue tusamitamab ravtansine	
Gastrointestinal Perforation	All Grades	Permanently discontinue ramucirumab	Consider benefit/risk for the patient to continue or delay tusamitamab ravtansine infusion	
Arterial Thromboembolic Events	All Grades	Definitively discontinue ramucirumab	Administer tusamitamab ravtansine as planned	
Wound Healing Complications	All Grades	Definitively discontinue ramucirumab for wound healing complications requiring medical intervention	Consider benefit/risk for the patient to continue or delay tusamitamab ravtansine infusion	

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.

Event	Symptoms severity (NCI CTCAE v5.0)	Management of IMP dosing (pembrolizumab)
Infusion-related reactions	Grades 1 or 2	Interrupt or slow the rate of infusion
	Grades 3 or 4	Permanently discontinue
Immune-mediated pneumonitis	Grade 2	Withhold
	Grades 3 or 4 or recurrent Grade 2	Permanently discontinue
Immune-mediated colitis	Grades 2 or 3	Withhold
	Grade 4 or recurrent Grade 3	Permanently discontinue
Immune-mediated hepatitis	AST or ALT greater than 3 but no more than 5 times the ULN or total bilirubin greater than 1.5 but no more than 3 times the ULN	Withhold
Immune-mediated endocrinopathies	Grades 3 or 4	Withhold until clinically stable
Immune-mediated nephritis	Grade 2	Withhold
	Grades 3 or 4	Permanently discontinue
Immune-mediated skin adverse reactions	Grade 3 or suspected Stevens-Johnson Syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold
	Grade 4 or confirmed SJS or TEN	Permanently discontinue
Other immune-mediated adverse reactions	Grades 2 or 3 based on the severity and type of reaction	Withhold
	Grade 3 based on the severity and type of reaction or Grade 4	Permanently discontinue
Recurrent immune-mediated adverse reactions	Recurrent Grade 2 pneumonitis Recurrent Grades 3 or 4	Permanently discontinue
Inability to taper corticosteroid	Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks after last dose of pembrolizumab	Permanently discontinue
Persistent Grade 2 or 3 adverse reaction (excluding endocrinopathy)	Grades 2 or 3 adverse reactions lasting 12 weeks or longer after last pembrolizumab	Permanently discontinue

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

For additional guidelines, please refer to ASCO Guidelines published in 2021 (24).

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 (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) 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

Not applicable.

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

Details provided in bibliographic reference 25.

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 categorization criteria are summarized in Table 19.

Table 19 - 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 actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

- CR: Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).
- Non-CR/Non-PD: Persistence of 1 or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- PD: 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 20 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

Table 20 - 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 21 is to be used.

Table 21 - 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 DOR 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 (SD) 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 tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228-47 (25).

10.8 APPENDIX 8: COUNTRY-SPECIFIC REQUIREMENTS

Serology for HBsAg and HCV and HIV test at screening will be performed only if required at the country level.

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

Table 22 - List of CYP substrates with narrow therapeutic range

Narrow Therapeutic Range (NTR) Substrates of CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A *in vivo*	
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 23 - List of strong (substrate AUC ratio ≥5) CYP3A inhibitors

CYP3A inhibitors	Precipitant Therapeutic Class	Victim (oral, unless otherwise specified)	AUC Ratio
VIEKIRA PAK	Antivirals	Tacrolimus	55.76
Telaprevir	Antivirals	Midazolam	13.50
Indinavir/RIT	Protease inhibitors	Alfentanil	36.50
Tipranavir/RIT	Protease inhibitors	Midazolam	26.91
Ritonavir	Protease inhibitors	Midazolam	26.41
Cobicistat	Pharmacokinetic Enhancer	Midazolam	19.03
Indinavir	Protease inhibitors	Vardenafil	9.67
Ketoconazole	Antifungals	Midazolam	17.08
Troleandomycin	Antibiotics	Midazolam	14.80
Saquinavir/RIT	Protease inhibitors	Midazolam	12.48
Itraconazole	Antifungals	Midazolam	10.80
Voriconazole	Antifungals	Midazolam	9.63
Mibefradil	Calcium Channel Blockers	Midazolam	8.86
Clarithromycin	Antibiotics	Midazolam	8.39
Danoprevir/RIT	Antivirals	Midazolam	13.42
Lopinavir/RIT	Protease inhibitors	Alfentanil	11.47
Elvitegravir/RIT	Treatments of AIDS	Midazolam	12.80
Posaconazole	Antifungals	Midazolam	6.23
Telithromycin	Antibiotics	Midazolam	6.20
Conivaptan	Vasopressin AntagonistsDiuretics	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	10.40
Ceritinib	Kinase Inhibitors	Midazolam	5.42
Ribociclib	Kinase Inhibitors	Midazolam	5.17
Josamycin	Antibiotics	Ivabradine	7.70
Tucatinib	Kinase Inhibitors	Midazolam	5.74
Lonafarnib	Other	Midazolam	7.39

List extracted from the Drug Interaction Database from the University of Washington (Home page: www.druginteractioninfo.org), updated in July 2022 and from FDA (https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm) updated in June 2020.

Abbreviations: AIDS=Acquired immune deficiency syndrome, AUC=Area under the curve, CYP=Cytochrome P450, RIT=Ritonavir.

10.11 APPENDIX 11: CONTINGENCY MEASURES FOR A REGIONAL OR NATIONAL EMERGENCY THAT IS DECLARED BY A GOVERNMENTAL AGENCY

For European countries contingency measures are currently only applicable for COVID-19 pandemic.

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.

10.11.1 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. Required protection of personal data (including security of e-mail interactions) and confidentiality of study data should be ensured.

If remote prescreening is planned to be implemented at site:

- The Investigator/delegate should contact each participant to inquire regarding the participant's willingness to participate in the prescreening process.
- If participant agrees to prescreening, the Investigator/delegate should send the prescreening ICF via e-mail to the participant's personal e-mail address (as allowed by local regulation) or by postal mail. The Investigator/delegate should provide an overview of the study (eg, tusamitamab ravtansine mechanism of action; design of the study in terms of treatment groups, visits, and prescreening procedures; and rationale for assessment of circulating CEA and 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 collect a blood sample for local measurement of circulating CEA and prepare and send the slides for CEACAM5 assessment.

10.11.2 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.

10.11.3 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 participant in Part 2 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.

10.11.4 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 capacity to perform the assessments.

As part of a site's contingency plan, a back-up site should be identified in advance in the case that the site delegated to perform the radiological tumor assessment is prevented from performing the

assessment by a regional or national emergency situation (eg, COVID-19 outbreak). The Investigator should ensure that the back-up site conducts the RECIST assessment in same manner as that used for baseline tumor assessments.

In the case that the primary tumor assessment site is incapacitated, ongoing patients would then be referred to the back-up site for tumor assessment. The Investigator/delegate should ensure the information on baseline assessment methods is shared with the back-up site's radiologist to ensure same method is followed for scans to be sent to IRC.

10.11.5 Statistical analyses and deviation

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

10.12 APPENDIX 12: PROTOCOL AMENDMENT HISTORY

The "Protocol Amendment Summary of Changes Table" for the current amendment is located directly before the Table of Contents (TOC).

Amended protocol 01: (12 November 2020)

This amended protocol 01 (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 because it significantly impacts the design of the study.

Overall Rationale for the Amendment

The purposes of this amendment are to clarify inclusion criteria/exclusion criteria (IC3, IC5, EC21, EC11); to update the safety guidelines; to introduce DLT as an adverse event of special interest (AESI); to introduce and clarify agreements regarding the future use of samples and data; and to add information concerning contingency measures in the case of an emergency such as a pandemic.

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, Table 2; 9.4.1 Efficacy analyses, Table 11	Modified tertiary/exploratory objective to include evaluation of circulating CEA at prescreening, and modified endpoint to include assessments of CEA at prescreening and screening, as well as during treatment	To reflect addition of new CEA assessment at prescreening

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis, Intervention groups and duration; 1.3.1 Study Flowchart, footnote **d;** 4.1 Overall design; 7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal; 8.1 Efficacy assessments	Add ±7 day window at follow-up visits specified after the last tumor assessment	For clarity
1.1 Synopsis, Study interventions; 6.1 Study interventions administered: IMP and Non-IMP	Moved heading for non-IMP medications to before premedication; changed to Noninvestigational medicinal products	For clarity
1.1 Synopsis: Main analysis populations and Section 9.3 Populations for analyses	Clarified definition of Activity population	For clarity
1.3.1 Study Flow Chart; 8.6 Pharmacodynamics	Added assessment of circulating CEA at prescreening	To reflect new prescreening assessment
1.3.1 Study Flow Chart, footnote **a**; 10.11 Appendix 11: Contingency measures for a regional or national emergency that is declared by a governmental agency	Modified statement regarding prescreening informed consent to reflect new requirement of circulating CEA assay results at prescreening	To reflect new prescreening Informed Consent form (ICF) requirement
1.3.1 Study Flow Chart; 8.8 Biomarkers	Added preinfusion IgG sample at Cycle 1	To explore the impact of IgG on PK parameters
1.3.1 Study Flow Chart	Collection of NSCLC charactaristics added for prescreening; footnote ***f*** updated to specify that only PD-1 status is collected prescreening	For clarity
1.3.1 Study Flow Chart	Footnote ***a*** updated to clarify that prescreening informed consent is not required for participants with known CEACAM5 status	For clarity
1.3.1 Study Flow Chart, footnote **n**; 8.2.4.1 Electrocardiograms	Specified timing window of 30 min after end of first IMP infusion at Cycle 1 for postinfusion ECG	For clarity
2.3 Benefit/Risk Assessment	Information regarding potential risks of tusamitamab ravtansine modified; added description of ramucirumab mechanism of action	To provide up-to-date information regarding potential risks to participants
4.1 Overall design	Clarified requirements for safety follow-up visits	For clarity
4.1 Overall design; 5.1 Inclusion Criterion I05	Reduced required number of tumor tissue slides for prescreening CEACAM status from 7 to 5.	To reflect actual analysis processing requirement
5.1 Inclusion criteria, I03	Modified criterion and clarified wording to specify that both sub criteria a and b should be met at study entry	For clarity
5.2 Exclusion criteria, E11	Added LVEF<50% as criterion for clinically relevant congestive heart failure	For clarity
5.2 Exclusion criteria, E21	Corrected to exclude >1 line of prior chemotherapy in metastatic setting	For clarity
5.4 Screen failures.	Added requirements for re-screening and emergency contingencies	To reflect and define operational process

Section # and Name	Description of Change	Brief Rationale
6.6.1 Part 1 (Safety run-in)	Added footnote for Table 6 Dose Reduction for Phase 1 part (safety run-in) to clarify how to proceed to treat patients initially at starting dose DL in the Part 1	For clarity
8 Study assessments and procedures	Removed references to histology, smoking status, medical history, and demography from statement regarding information to be collected from prescreening failures	To reflect operational process, as these data are not collected from prescreening failures
8.2.6.2 Ocular toxicity	Specified periodic ocular exams to follow participants presenting with ocular toxicity	For clarity of safety management guidelines
8.2.6.10 Peripheral neuropathy	new section with guidance for managing peripheral neuropathy	For clarity of safety management guidelines
8.2.6.11 Colitis (including hemorrhagic)	New section for managing GI toxicity	For clarity of safety management guidelines
8.3.1 Adverse events, treatment-emergent adverse events, and adverse events of special interest	Protocol-defined DLT added as AESI	For safety analysis
8.11 Use of biological samples and data for future research	New section to describe consent to store samples for future studies	To comply with Sanofi policy and procedures
9.4.2 Safety analyses	Reworded definition of prescreening period	For clarity
10.1.3 Informed consent process	Added details regarding ICF and process	To comply with Sanofi policy and procedures
10.4 Appendix 4: Recommended supportive care and/or dose modification guidelines for drug-related adverse events	Added clarifications for Grade 2, Grade 3, and Grad 4 ocular toxicity; added peripheral neuropathy (Grades 1-4); Neutrophil count decreased Grade 4; Grade 4 febrile neutropenia.	For clarity
10.4 Appendix 4: Recommended supportive care and/or dose modification guidelines for drug-related adverse events	Changed “Prematurely/Permanently” discontinue to “Definitively” discontinue for Hypertension, Hemorrhage, Proteinuria, Arterial thromboembolic events, and Wound healing complications	Consistency of terminology and clarity
10.5 Appendix 5: Contraceptive guidance and collection of pregnancy information	Deleted redundant wording for reporting of pregnancy	For clarity
New Appendix 11 (Section 10.11) referenced in Sections 4.1, 6, 7.1.2, 8, 9.4.3, and10.1.3	Addition of contingency measures to be implemented in the case of a regional or national emergency	To permit adaptation of study procedures in an emergency
New Appendix 12 (Section 10.12) to precede Abbreviations (now Appendix 13 [Section 10.13]);	Addition of Document History Appendix	Per Sanofi process
Throughout	Correction of typographical errors and standardization of wording	For clarity

10.13 APPENDIX 13: ABBREVIATIONS

ADC:	antibody-drug conjugate
AESI:	adverse event of special interest
AIDS:	acquired immunodeficiency syndrome
ALK:	anaplastic lymphoma kinase (gene)
ALP:	alkaline phosphatase
ALT:	alanine aminotransferase (SGPT)
ANC	absolute neutrophil count
ASCO:	American Society of Clinical Oncology
AST:	aspartate aminotransferase (SGOT)
ATA:	antitherapeutic antibody
ATE:	arterial thromboembolic event
BOR:	best overall response
BSA:	body surface area
CEA:	carcinoembryonic antigen
CEACAM5:	carcinoembryonic antigen-related cell adhesion molecule 5
CHF:	congestive heart failure
CI:	confidence interval
CONSORT:	Consolidated Standards of Reporting Trials
CR:	complete response
CRC:	colorectal cancer
CTCAE:	Common Terminology Criteria for Adverse Events
CYP:	cytochrome P_{450}
DL:	dose level
DLT:	dose-limiting toxicity
DOR:	duration of response
DCR	disease control rate
ECG:	electrocardiogram
ECOG:	Eastern Cooperative Oncology Group
eCRF:	electronic case report form
eGFR:	estimated glomerular filtration rate
EGFR:	epidermal growth factor receptor (gene)
EOI:	end of infusion
FDG-PET:	fluorodeoxyglucose-positron emission tomography
FFPE:	formalin-fixed, paraffin-embedded
FOLFIRI:	folinic acid/fluorouracil/irinotecan
GI:	gastrointestinal
G-CSF:	granulocyte colony-stimulating factor
HBsAg:	hepatitis B virus surface antigen
HCV:	hepatitis C virus
HRQOL:	health-related quality of life
HIV:	human immunodeficiency virus

IB:	Investigator's Brochure
ICI:	immune chekpoint inhibitors
ICF:	informed consent form
IEC:	independent ethics committee
IHC:	immunohistochemical
IMP:	investigational medicinal product
IRB:	institutional review board
IRR:	infusion-related reaction
IV:	intravenous
LVEF:	left ventricular ejection fraction
MDRD:	Modification of Diet in Renal Disease
MTD:	maximum tolerated dosee
MRI:	magnetic resonance imaging
MUGA:	multigated acquisition scan
NCI:	National Cancer Institute
NE:	not evaluable
NIMP:	non-investigational medicinal product
NSCLC:	non-small-cell lung cancer
NSQ NSCLC:	non-squamous, non-small-cell lung cancer
NTR:	narrow therapeutic range
ORR:	objective response rate
PD:	progressive disease
PD-L1:	programmed death ligand 1
PD-1:	programmed death-1
PFS:	progression-free survival
PK:	pharmacokinetic
PR:	partial response
PT:	preferred term
Q2W:	every 2 weeks
Q3W	every 3 weeks
RBC:	red blood cells
RD:	recommended dose
RECIST:	Response Evaluation Criteria in Solid Tumors
ROS1	ROS receptor tyrosine kinase 1 (gene)
RP2D:	recommended Phase 2 dose
SAE:	serious adverse event
SAP:	statistical analysis plan
SC:	Study Committee
SD:	stable disease
SOA:	schedule of assessements
SOC:	system organ class
TEAE:	treatment-emergent adverse event
ULN:	upper limit of normal
VEGF:	vascular endothelial growth factor

VEGFR-2:	vascular endothelial growth factor receptor-2
WBC	white blood cells
WOCBP:	woman of child-bearing potential

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