# AMENDED CLINICAL TRIAL PROTOCOL 06

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|---|---|
| **Protocol title:** | **Open-label, Phase 2 study of tusamitamab ravtansine (SAR408701) combined with pembrolizumab and tusamitamab ravtansine (SAR408701) combined with pembrolizumab and platinum-based chemotherapy with or without pemetrexed in patients with CEACAM5-positive expression advanced/metastatic nonsquamous non-small-cell lung cancer (NSQ NSCLC)** |
| **Protocol number:** | **ACT16146** |
| **Amendment number:** | **06** |
| **Compound number (INN/Trademark):** | **SAR408701**<br>**Tusamitamab ravtansine/Not applicable** |
| **Study phase:** | **Phase 2** |
| **Short title:** | **Tusamitamab ravtansine (SAR408701) in combination with pembrolizumab and tusamitamab ravtansine (SAR408701) in combination with pembrolizumab and platinum-based chemotherapy with or without pemetrexed in patients with NSQ NSCLC (CARMEN-LC05)** |
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| **Monitoring Team's Representative Name and Contact Information** | |

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**PROTOCOL AMENDMENT SUMMARY OF CHANGES**

# DOCUMENT HISTORY

| Document | Country/countries impacted by amendment | Date, version |
|---|---|---|
| Amended Clinical Trial Protocol 06 | All | 21 August 2023, version 3 (electronic 10.0) |
| Amended Clinical Trial Protocol 05 | All | 04 July 2022, version 1 (electronic 7.0) |
| Amended Clinical Trial Protocol 04 | All | 18 August 2021, version 1 (electronic 6.0) |
| Amended Clinical Trial Protocol 03 | All | 04 May 2021, version 1 (electronic 4.0) |
| Amended Clinical Trial Protocol 02 | All | 25 January 2021, version 1 (electronic 3.0) |
| Amended Clinical Trial Protocol 01 | All | 23 November 2020, version 1 (electronic 2.0) |
| Original Protocol | | 26 February 2020, version 1 (electronic 1.0) |

## Amended protocol 06 (21 Aug 2023)

This amendment (Amended protocol 06) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

# OVERALL RATIONALE FOR THE AMENDMENT

The main purpose of this amendment is to recruit additional participants to optimize dose selection for tusamitamab ravtansine when combined with pembrolizumab, with or without chemotherapy, by testing up to 2 lower tusamitamab ravtansine dose levels (DLs), in addition to the recommended dose for the expansion phase of the study (RDE).

**Protocol amendment summary of changes table**

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.1 Synopsis;<br>2.1 Study Rationale | Updated text to remove specific reference to Part A results, and updated the number of the first patients treated from 5 patients to 25 patients. | Preliminary efficacy data are presented in a more general manner appropriate for an ongoing study. |
| 1.1 Synopsis; 1.2 Schema;<br>3 Objectives and endpoints;<br>4.1.1 Safety run-in part: DLT observation period;<br>4.1.2 Expansion Cohorts (Parts A & C); 4.3 Justification for dose; 6.6.1 Determination of recommended doses;<br>9.1 Statistical hypotheses;<br>9.2 Sample size determination;<br>9.5 Interim analyses | "Recommended Phase 2 dose (RP2D)" replaced with "recommended dose for expansion (RDE)" | The goal of the Safety Run-In portion of this Phase 2 study is to find an appropriate tusamitamab ravtansine dose level for each combination regimen in the expansion phase of the study. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.1 Synopsis | Moved dose-limiting toxicity (DLT) decision tree and descriptive text from section describing DLT observation procedure in Part A, Part B, and Part C to a new synopsis subsection, "DLT observation period" following the Part C description; labeled the abbreviated sections describing each part under a new subheading, "Safety Run-in" | To simplify presentation of safety run-in and DLT procedures for all 3 parts of the study |
| 1.1 Synopsis; 3 Objectives and endpoints; 8.1 Efficacy assessments; 9.4.2 Primary endpoint; 9.4.3 Secondary endpoints | Updated primary objective to clarify that the goal of the Safety run-in is to determine appropriate tusamitamab ravtansine dose levels for evaluation in combination regimens in the expansion phase. | To specify distinct objectives of the Safety Run-in and Expansion parts |
| | Added a new primary objective for the Expansion to assess antitumor activity of combination treatment based on endpoint of objective response rate (ORR; proportion of participants with best overall responses of complete response [CR] or partial response [PR]). | |
| | Added new secondary objective to assess the antitumor activity at several dose levels (DLs) of tusamitamab ravtansine in combination regimens as assessed with 2 endpoints: progression-free survival (PFS) and disease control rate (DCR) | |
| | Updated secondary safety objective to reflect multiple tusamitamab ravtansine DLs) to be tested in each combination regimen. | |
| | New secondary objective and corresponding endpoints were added to assess the durability of the response to treatment with several tusamitamab ravtansine DLs in combination regimens as assessed by duration of response (DOR; time from first documented evidence of CR or PR until progressive disease [PD]). | |
| 1.1 Synopsis | Preliminary results of Part A are removed and repeated details describing the study population have been deleted from the overall design description. | To make the text more concise. |
| 1.3.1 Study procedures flowchart; 4.1 Overall design | Specified that PD-L1 status by an approved test will be collected "and assessed locally or centrally" and circulating CEA will be assessed locally; added corresponding footnote "a." | To clarify that prescreening tumor samples can be assessed either locally or centrally. |
| 1.1 Synopsis; 4.1 Overall design; New section 4.1.2 Expansion cohorts (Parts A & C); 9.2 Sample size determination | Specified the subheadings of "Safety run-in" and/or "Expansion" for Parts A, B, and C for Synopsis overall design, and added new subsection 4.1.2 for Parts A and C. | To clarify the description of study design |
| 1.1 Synopsis; New section 4.1.2 Expansion cohorts (Parts A & C) | Specified that in Parts A and C, 20 participants would be treated at the RDE and at least 20 participants at 1-2 lower dose levels with early stopping rules, Updated the planned total number of participants for Parts A, B, and C. | To reflect changes to optimize tusamitamab ravtansine dose selection for each combination |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.1 Synopsis; New subsection 4.1.1 Safety run-in part: DLT observation period | Specified each quadruplet platinum combination for Part C as tusamitamab ravtansine, pembrolizumab, pemetrexed, and either cisplatin or carboplatin. | To specify the actual combinations of treatments administered |
| | Added explanation that if the quadruplet combination investigated in Part C is shown to have an acceptable toxicity profile, enrollment to the triplet treatment in Part B could be stopped. | To clarify that triplet treatment would be fully evaluated in Part B only in the case that the quadruplet regimen in Part C was not well tolerated. |
| 1.1 Synopsis; 4.1 Overall design; 4.3 Justification of dose; 6.1 Study interventions administered; 6.6.2 Individual dose modifications | Added text for dose regimen to test lower dose of tusamitamab ravtansine 100 mg/m$^2$ Q3W (added lower DL in Table 2 and Table 5). | To clarify decision process to optimize dose selection of tusamitamab ravtansine when combined with pembrolizumab with or without chemotherapy. |
| 1.1 Synopsis; 9.4.1 General considerations | Added cut-off for secondary endpoints including DOR and PFS. | Additional cut-off for these newly added secondary endpoints to demonstrate antitumor activity over longer follow-up times. |
| | Added statement specifying that study cut-offs will occur by parts, and could be grouped if the different cut-off dates for the primary endpoint are close. | Clarification |
| 1.1 Synopsis; 9.2 Sample size determination | Updated statistical considerations for sample size calculations for Part A, Part B, and Part C. | To optimize the dose selection of tusamitamab ravtansine when combined with pembrolizumab with or without chemotherapy. |
| 1.1 Synopsis; 9.4.1 General considerations | Specified that ORR, DCR, DOR, and PFS will be summarized by part, DL and overall. | Clarification of planned analyses of antitumor activity. |
| 1.1 Synopsis; 9.2 Sample size determination; 9.4.2.2 Objective response rate | Specified Clopper-Pearson method for calculating the confidence interval for ORR | To provide details of planned analyses |
| 1.1 Synopsis; 9.4.2.2 Secondary endpoints | Added analysis description for secondary endpoints: DOR, PFS, and DCR. | To describe planned analyses of newly added secondary efficacy endpoints. |
| 1.2 Schema | Updated Figure 2, Figure 3, and Figure 4 with details participants numbers and parts details. | To reflect the new study design and population. |
| 1.1 Synopsis; 1.3.1 Study procedure flowcharts; 4.1.3 Duration of the study; 8.1 Efficacy assessments | Added description of timing for tumor assessments for a participant who stopped treatment before documented progressive disease in text and footnote “e” in the SOA. | To clarify tumor assessment procedures. |
| 1.1 Synopsis; 3 Objective and endpoints; 1.3.2.1 PK/ATA flow chart for Part A; 1.3.2.2 PK/ATA flow chart for Part B; 1.3.2.3 PK/ATA flow chart for Part C; 8.4 Pharmacokinetics | Added “SAR408701, DM4, and Me-DM4” in parenthesis for PK sample ID in Tusamitamab ravtansine. Added footnote “f” for this heading to mention that DM4 and Me-DM4 to be collected only for patients enrolled from amendment #6. | DM4 and Me-DM4 will be assessed in addition to SAR408701 for new participants enrolled. |
| 1.1 Synopsis; 4.1.2 Expansion cohorts (Parts A&C) | Clarified that the expansion phase of Part A was dependent on the benefit/risk assessment of the participants treated at RDE in Part A and of participants treated at a lower dose in Part C | To make clear that implementation of the expansion phase is contingent on safety in the Safety Run-in |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.3.1 Study procedure flowcharts | Added new row for "FFPE sections for RNA and DNA analysis" and corresponding footnote "o" and "p". | To explore potential sets of biomarkers besides target expression that could be predictive. |
| 2.1 Study rationale | Clarified the wordings from "no overlap is expected" to "no overlapping toxicities are expected". | Clarification. |
| 3 Objectives and endpoints | Added new tertiary/exploratory objective to explore tumor DNA and RNA as potential prognostic biomarkers of response to treatment | To explore potential sets of biomarkers besides target expression that could be predictive of response. |
| | Added new tertiary/exploratory objective to explore PK -PD relationship of tusamitamab ravtansine d with safety and efficacy endpoints. | To have additional data for understanding of PK-PD relationships |
| 1.1 Synopsis; 4.1 Overall design; new subsections 4.1.1 Safety run-in part: DLT observation period; 4.1.2 Expansion cohorts (Parts A & C)" | Described design and updated numbers of participants in the Safety Run-In Part (DLT observation period); details of study design for the expansion cohorts (Parts A & C) at the RDE and lower dose level(s) ; and added new level 3 headings. | Clarification of study design. |
| 4.3 Justification for dose | Rationale added for decrease to the lower DL 150 mg/m$^2$ Q3W that would be the recommended for the expansion part in all cohorts. Additionally, a lower dose of 100 mg/m$^2$ will also be tested. | Addition of rationale for new DLs. |
| 5.1 Inclusion criteria | Added inclusion criterion for life expectancy of at least 3 months | To ensure meaningful follow-up of safety and efficacy for each participant. |
| 5.2 Exclusion criteria, 6.5 Concomitant therapy, 10.8 Appendix 8 Strong CYP3A inhibitors | Removed exclusion criterion for a medical condition requiring concomitant administration of a medication metabolized by CYP450 with a narrow therapeutic window.<br>Removed Table of list of CYP substrates with narrow therapeutic range from appendix. | Consistency with Investigator's brochure Edition 9 |
| 6.6.1 Determination of recommended doses; Table 4: Dose levels (safety run-in part) | Clarified the phase of the study as "safety run-in phase" during DLT observation period. | To include new DL, 100 mg/m$^2$ |
| | Specified that 100 mg/m$^2$ and 150 mg/m$^2$ doses will be tested in expansion cohorts for Parts A and C. | |
| 6.8 Treatment of overdose | Changed the section number from 8.4 to 6.8 and updated the text as per new template. | To conform to new template requirement |
| 8 Study assessments and procedures | Statement describing contingencies for procedures in the case of an emergency and referring to appendix detailing these contingencies was added as required by new template | Template update. |
| 8.1 Efficacy assessments | Updated text with the details of assessment for antitumor activity.<br>Updated text with more specific reason for ending the assessment. | To reflect the addition of secondary efficacy endpoints (DOR, PFS, and DCR). |
| New section 8.3.9 Overdose, medication errors, misuses or abuses of medicinal product | Section defining overdose, medical error, and misuse added as per new template. | To conform to new template requirements |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 8.4 Pharmacokinetics | Clarified that samples collected for analyses of tusamitamab ravtansine concentration may also be used to evaluate the relationship of exposure to additional safety or efficacy parameters or for testing analytical method performance | To identify additional analyses of the relationship of pharmacokinetic exposure to safety and efficacy |
| New subheadings 8.6.1 Plasma cfDNA and 8.6.2 Tumor DNA and RNA analyses | New subsections added to describe analyses of RNA and DNA in plasma and tumor tissue. | To clarify DNA and RNA assessment procedures |
| 8.8 Immunogenicity assessments | Added brief description of approach to screening for, confirming, and further characterizing treatment emergent antitherapeutic antibodies (ATA). | To explain the strategy for ATA management. |
| 8.10 Use of biological samples and data for future research | Section updated as per new template. | Template update. |
| 9.1 Statistical hypothesis | Updated the text with details of safety run-in and expansion for Parts A, B, and C. | To reflect the addition of efficacy primary endpoint and dose optimization. |
| 9.2 Sample size determination | Added Table 7- Estimated objective response rate (ORR) and confidence interval depending on number of responders. | To optimize the dose selection of tusamitamab ravtansine when combined with pembrolizumab with or without chemotherapy. |
| 9.2 Sample size determination | Updated text to clarify enrollment based on an interim analysis of objective responses in Part A and Part C dose expansion | To clarify estimates of participants to be enrolled at each DL based on an interim analysis |
| 9.4.1 General considerations | Cut-off for analysis of ORR was restricted to Parts A and C, for which ORR is now a primary endpoint. A statement was added to explain that the ORR cut-off could be defined upon completion of enrollment in a given DL. | To reflect the addition of participants with a lower dose 100 mg/m². |
| 9.4.3.8 Pharmacokinetic variables | Described planned analyses of PK, population PK, and PK-PD analyses. | To reflect the changes in PK analyses |
| 9.5 Interim analyses | Added detailsbing interim analyses of objective responses in Part A and Part B. | To clarify that interim analyses are planned in expansion Part A and Part C to confirm adequate responses in 10 participants treated at a lower DL before enrolling another 10 participants at that DL |
| 10.1 Appendix 1 Regulatory, Ethical, and Study Oversight considerations | Regulatory and ethical considerations, data protection, Protection of personal data, and Dissemination of clinical study data updated as per new template. | To comply with new protocol template requirements |
| 10.3 Appendix 3 Adverse events: definitions and procedures for recording, evaluating, follow-up, and reporting | Section updated as per new template. | To comply with new protocol template requirements |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 10.5 Appendix 5 Genetics | Updated text for RNA sample handling and storage. | To explore potential sets of biomarkers besides target expression that could be predictive of response and explain handling and storage of the samples. |
| 10.8 Appendix 8 Strong CYP3A inhibitors | In Table 14, vardenafil was replaced with midazolam, and information on potent CYP3A Inhibitors was added. | For consistency with updated information for known CYP3A4 inhibitors |
| 10.11 Appendix 11: Contingency measures for a regional or national emergency that is declared by a governmental agency | Section updated as per new template. | To comply with new protocol template requirements |
| Throughout the document | Correction of typographical errors and standardization of wording. | For clarification |

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# 1 PROTOCOL SUMMARY

## 1.1 SYNOPSIS

**Protocol title:** Open-label, Phase 2 study of tusamitamab ravtansine (SAR408701) combined with pembrolizumab and tusamitamab ravtansine (SAR408701) combined with pembrolizumab and platinum-based chemotherapy with or without pemetrexed in patients with CEACAM5-positive expression advanced/metastatic nonsquamous non-small-cell lung cancer (NSQ NSCLC)

**Short title:** Tusamitamab ravtansine (SAR408701) in combination with pembrolizumab and tusamitamab ravtansine (SAR408701) in combination with pembrolizumab and platinum-based chemotherapy with or without pemetrexed in patients with NSQ NSCLC (CARMEN-LC05)

**Rationale:**

Most patients with NSCLC present with an advanced cancer stage at the time of diagnosis. Despite recent progress in the treatment of advanced/metastatic NSCLC, there remains a need for effective new treatment at the time of disease progression.

Tusamitamab ravtansine is an antibody conjugate to the cytotoxic maytansinoid agent DM4. In an ongoing Phase 1 study (TED13751), tusamitamab ravtansine has demonstrated meaningful preliminary antitumor activity in patients heavily pretreated for NSQ NSCLC with high CEACAM5 expression.

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 combination with platinum-based chemotherapy with no epidermal growth factor receptor (*EGFR*) or anaplastic lymphoma kinase (*ALK*) genomic tumor aberrations, and in Stage III when patients are not candidates for surgical resection or definitive chemoradiation, or metastatic (1).

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

Encouraging preliminary efficacy data of ongoing ACT16146 study have been observed in the first 25 patients treated in the study. The results observed in TED13751 where tusamitamab ravtansine was administered as monotherapy at 100 mg/m² Q2W in patients with CEACAM5 expression ≥1% and these preliminary efficacy data from Part A where tusamitamab ravtansine is administered in combination with pembrolizumab in patients with CEACAM5 expression ≥50% support a decrease in threshold of CEACAM5 expression from 50% to 1%.

The objective of this study is to evaluate the safety and antitumor activity (efficacy) of tusamitamab ravtansine in combination with pembrolizumab and tusamitamab ravtansine in combination with pembrolizumab and platinum-based chemotherapy (Investigator's choice of cisplatin or carboplatin) and tusamitamab ravtansine in combination with the standard of care for first-line treatment, pembrolizumab, platinum-based chemotherapy, and pemetrexed in NSQ NSCLC participants with CEACAM5 high or moderate expression in tumors (high expression is defined as CEACAM5 immunohistochemistry [IHC] intensity ≥2+ in ≥50% of tumor cells and moderate expression is defined as intensity ≥2+ in ≥1% and <50% of tumor cells).

## Objectives and endpoints

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • Safety run-in part: to assess the tolerability and to determine the recommended doses of tusamitamab ravtansine in combination with pembrolizumab and tusamitamab ravtansine in combination with pembrolizumab and platinum-based chemotherapy with or without pemetrexed to be tested in the expansion part of the study in the NSQ NSCLC population | • Incidence of study drug-related dose-limiting toxicity (DLTs) at Cycle 1 (C1D1 to C1D21), including but not limited to corneal toxicity |
| • Expansion part (including participants treated at the recommended dose for expansion [RDE] from the Safety Run-in part): to assess the antitumor activity of several dose levels (DLs; if applicable) of tusamitamab ravtansine in combination with pembrolizumab and of several DLs of tusamitamab ravtansine in combination with pembrolizumab, platinum-based chemotherapy, and pemetrexed in the NSQ NSCLC population | • Objective response rate defined as proportion of participants who have a confirmed complete response (CR) or partial response (PR) as best overall response per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (2) |
| **Secondary** | |
| • To assess the safety and tolerability of several DLs (if applicable) of tusamitamab ravtansine in combination with pembrolizumab and of 1 DL of tusamitamab ravtansine in combination with pembrolizumab and platinum-based chemotherapy, and of several DLs of tusamitamab ravtansine in combination with pembrolizumab and platinum-based chemotherapy with pemetrexed in the NSQ NSCLC population | • Incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and laboratory abnormalities according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) V5.0 |
| • To assess the antitumor activity of several DLs (if applicable) of tusamitamab ravtansine in combination with pembrolizumab and of 1 DL of tusamitamab ravtansine in combination with pembrolizumab and platinum-based chemotherapy, and of several DLs of tusamitamab ravtansine in combination with pembrolizumab, platinum-based chemotherapy, and pemetrexed in the NSQ NSCLC population | • Progression-free survival (PFS), 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 (not for Part B).<br>• Disease control rate (DCR), defined as the percentage of participants who have achieved confirmed CR, confirmed PR, or stable disease (SD) as best overall response (BOR) per RECIST v1.1 |

| Objectives | Endpoints |
|---|---|
| • To assess the durability of the response to treatment with several DLs (if applicable) of tusamitamab ravtansine in combination with pembrolizumab and of 1 DL of tusamitamab ravtansine in combination with pembrolizumab and platinum-based chemotherapy, and of several DLs of tusamitamab ravtansine in combination with pembrolizumab, platinum-based chemotherapy, and pemetrexed in the NSQ NSCLC population | • 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 the antitumor activity of tusamitamab ravtansine in combination with pembrolizumab and platinum-based chemotherapy in the NSQ NSCLC population | • Objective response rate, defined as proportion of participants who have a confirmed CR or PR as per BOR per RECIST v1.1 (2) |
| • To assess the pharmacokinetics (PK) of tusamitamab ravtansine, pembrolizumab, pemetrexed, cisplatin, and carboplatin, each when given in combination as a doublet (tusamitamab ravtansine + pembrolizumab) or a triplet (tusamitamab ravtansine + pembrolizumab + platinum-based chemotherapy) or a quadruplet (tusamitamab ravtansine + pembrolizumab + platinum-based chemotherapy + pemetrexed) | • Pharmacokinetic concentrations of tusamitamab ravtansine (SAR408701, DM4, Me-DM4), pembrolizumab, pemetrexed, cisplatin, and carboplatin. |
| • To assess the immunogenicity of tusamitamab ravtansine in combination with pembrolizumab and tusamitamab ravtansine in combination with pembrolizumab and platinum-based chemotherapy with or without pemetrexed | • Incidence of antitherapeutic antibodies (ATAs) against tusamitamab ravtansine |

**Overall design:**

This is a Phase 2, open-label, multicenter study.

CEACAM5 expression will be assessed by IHC during the prescreening phase and participants with NSQ NSCL CEACAM5 high expression (≥50%) or moderate expression (≥1% and <50%) tumors will go through protocol screening procedures. They will be enrolled in Part A, Part B or Part C per Investigator's choice.

***SAFETY RUN-IN***

**PART A:**

The tolerability and safety of the tusamitamab ravtansine and pembrolizumab combination will be assessed.

The first 3 participants will receive, Q3W, a 200 mg pembrolizumab infusion followed by a tusamitamab ravtansine infusion at the starting dose of 150 mg/m².

The tolerability of the doublet combination will be assessed in approximately 6 to 18 participants to determine the recommended dose for expansion (RDE).

**PART B:**

The tolerability and safety of the pembrolizumab, tusamitamab ravtansine, and platinum-based chemotherapy combinations will be assessed. Participants can be assigned to either cisplatin or carboplatin, per Investigator choice.

Participants will receive Q3W pembrolizumab 200 mg + tusamitamab ravtansine (150 mg/m², 170 mg/m², or 120 mg/m²) + cisplatin 75 mg/m² or carboplatin AUC 5, all on Day 1 for the first 4 cycles, followed by Q3W pembrolizumab 200 mg + tusamitamab ravtansine (150 mg/m², 170 mg/m², or 120 mg/m²) on Day 1 of subsequent cycles.

The tolerability of each triplet platinum combination will be assessed in approximately 6 to 18 participants to determine the RDE in each triplet platinum combination arm (carboplatin or cisplatin).

If the quadruplet combination investigated in Part C has an acceptable toxicity profile, and as the triplet combination was explored in Part B only in case the quadruplet would not be well tolerated, enrollment in Part B will be stopped as soon as the Safety Run-In for Part C ends.

**PART C:**

The tolerability and safety of the tusamitamab ravtansine, pembrolizumab, platinum-based chemotherapy, and pemetrexed combinations will be assessed. Participants can be assigned to either cisplatin or carboplatin, per Investigator choice.

Participants will receive Q3W pembrolizumab 200 mg + tusamitamab ravtansine (150 mg/m², 170 mg/m², or 120 mg/m²) + pemetrexed 500 mg/m² (with vitamin supplementation) + cisplatin 75 mg/m² or carboplatin AUC 5, all on Day 1 for the first 4 cycles, followed by Q3W pembrolizumab 200 mg + tusamitamab ravtansine (150 mg/m², 170 mg/m², or 120 mg/m²) + pemetrexed 500 mg/m$^2$ (with vitamin supplementation) on Day 1 of subsequent cycles.

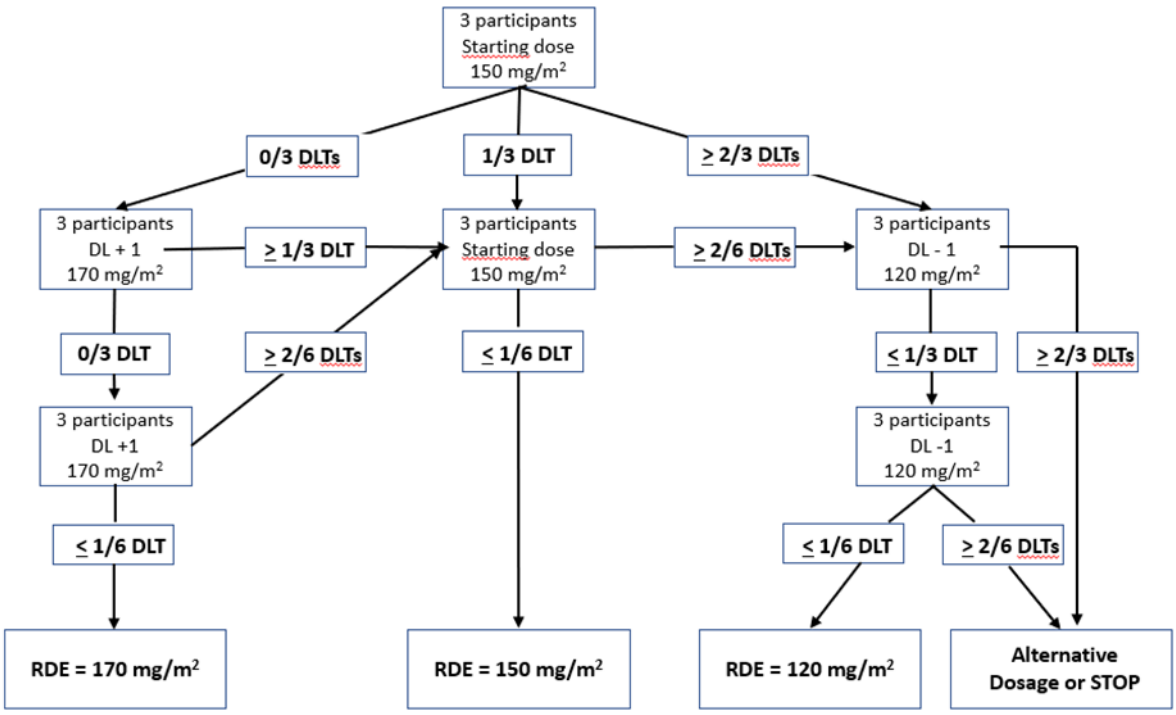
The tolerability of each quadruplet platinum combination (ie, tusamitamab ravtansine, pembrolizumab, pemetrexed, and either cisplatin or carboplatin) will be assessed in approximately 6 to 18 participants to determine the RDE.

**Dose-limiting toxicity observation period:**

The DLT observation period is the first cycle (21 days). Depending on the DLTs observed, up to 3 dose levels (DLs) of tusamitamab ravtansine can be tested: 150 mg/m², 170 mg/m², and 120 mg/m².

For each DL of the combination arm (starting dose, DL plus 1 [DL +1], and DL minus 1 [DL -1] if applicable), a minimum of 1 week is mandatory between the first dose of the first participant treated at this DL and the first dose of the next participant treated at the same DL. Once 3 participants have been treated at this DL and are DLT-evaluable, the tolerability of the combination is assessed according to the following algorithm as illustrated in Figure 1.

**Figure 1 - Decision tree for tusamitamab ravtansine dose in Part A, Part B, and Part C**




DL: dose level; DLT: dose-limiting toxicity; RDE: recommended dose for expansion
Note: In case of 2 or more DLTs at DL -1, the study part may be stopped or the dosage reconsidered.
The RDE dose is based on DLTs as well as the totality of the data, including overall safety, efficacy, and PK-PD modeling.

## *EXPANSION (PARTS A & C)*

The Expansion Phase will determine the recommended dose for Phase 3 studies for Parts A and C based on safety, efficacy, and PK-PD modeling of at least 2 DLs of tusamitamab ravtansine, as detailed below.

- In Part A, at least 20 participants will be treated at the RDE (150 mg/m$^2$ and at least 20 participants will be treated at a lower DL (100 mg/m$^2$). An optional 10 participants may be treated at an additional DL after these cohorts are completed.
  - If fewer than 3 of 10 participants at 100 mg/m$^2$ have a confirmed objective response, early stopping rules will be applied, such that enrollment at this DL will be stopped, and at least 20 participants will then be treated at an intermediate DL (120 mg/m$^2$). If the 100 mg/m$^2$ DL is not stopped early, enrollment will continue at this DL to treat at least 20 participants.

- In Part C, at least 20 participants will be treated at the RDE (150 mg/m$^2$) and at least 20 participants will be treated at a lower DL (100 mg/m$^2$). An optional 10 participants may be treated at an additional DL after these cohorts are completed.

  If fewer than 4 of 10 participants at 100 mg/m$^2$ have a confirmed objective response, early stopping rules will be applied, such that enrollment at this DL will be stopped, and at least

20 participants will then be treated at an intermediate DL (120 mg/m$^2$). If the 100 mg/m$^2$ DL is not stopped early, enrollment will continue at this DL to treat at least 20 participants.

- Enrollment of a participant into Part C or A will be based on the Investigator's choice.

For each part, expansion cohorts will be opened for enrollment after completion of the Safety Run-in for the considered part. Opening of each cohort and enrollment of participants in each cohort will be defined by the Sponsor based on discussions with the Study Committee.

**Disclosure Statement**: This is a parallel group treatment with 5 arms and no masking.

**Number of participants:**

**In Part A**, the actual sample size could vary depending on DLTs observed. It is anticipated that 6 to 62 participants will be treated with tusamitamab ravtansine + pembrolizumab: up to 12 DLT-evaluable participants at a DL other than RDE in the safety run-in; at least 20 participants at the RDE (including 6 participants at the RDE from the safety run-in); 20 to 30 participants at lower DL(s), and optional 10 patients at an additional DL.

**In Part B,** the actual sample size could vary depending on DLTs observed. It is anticipated that in each triplet combination arm, 6 to 18 participants will be treated with tusamitamab ravtansine + pembrolizumab + cisplatin or carboplatin: up to 12 DLT-evaluable participants in each triplet combination arm treated at a DL other than the RDE, and 6 DLT-evaluable participants in each triplet combination arm treated at the RDE.

**In Part C**, the actual sample size could vary depending on DLTs observed. It is anticipated that overall, 12 to 74 participants will be treated with tusamitamab ravtansine + pembrolizumab + pemetrexed + cisplatin or carboplatin: up to 12 DLT-evaluable participants in each quadruplet combination arm treated at a DL other than the RDE; at least 20 participants at the RDE (including participants at the RDE from the safety run-in); at least 20 participants at the RDE (including 6 participants at the RDE from the safety run-in); 20 to 30 participants at lower DL(s), and optional 10 patients at an additional DL.

**Study periods and duration:**

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

- **Screening period:** up to 28 days.
- **Treatment period:** once successfully screened, enrolled participants may receive study intervention 4 cycles of cisplatin or carboplatin (Part B and C), and pemetrexed (Part C), and tusamitamab ravtansine and pembrolizumab until confirmed disease progression, unacceptable toxicity, new anticancer therapy initiation, death, or the participant's or investigator's decision to stop the treatment. Each cycle of treatment will last for 3 weeks. After discontinuing study intervention, participants will return to the study site approximately 30 days (±5 days) after the last IMP administration or before the participant receives another anticancer therapy, whichever is earlier, for end of treatment (EOT) assessments.

- **Safety follow-up visit:** will be performed 90 days (±7 days) after the last IMP administration.
- Tumor assessments will be performed at baseline, every 6 weeks for the first 24 weeks from C1D1, then every 9 weeks until radiological disease progression, death, the data cut-off date for the secondary endpoints, initiation of further anticancer therapy, or withdrawal of participant's consent, whichever comes first. Participants who stopped treatment before documented progressive disease (PD) should also undergo tumor assessments.

The cut-off date for each interim analysis on the primary endpoint (ORR) in Part A and Part C corresponds to the date on which the first 10 participants treated at the lower DL (100 mg/m$^2$) have had at least 2 postbaseline tumor assessments, experienced confirmed objective response, or have discontinued the study for any reason.

The study cut-off for the primary endpoint (ORR) corresponds to the date on which all-treated participants have had at least 2 postbaseline tumor assessments, experienced confirmed objective response, or have discontinued the study for any reason. This study cut-off will occur by part (Parts A & C) unless the respective cut-off dates are close together, and will be approximately 4.5 months (3 months for 2 tumor assessments, and 1.5 months if a confirmation of response is needed) after the date of the first IMP administration of the last participant in each part.

The cut-off for the secondary endpoints including DOR and PFS will be approximately 6 months after the cut-off date for the primary endpoint.

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

## Study interventions

*Investigational medicinal products*

Study interventions include pembrolizumab, tusamitamab ravtansine, cisplatin, carboplatin and pemetrexed.

### *Pembrolizumab*

Pembrolizumab will be administered prior to administration of 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.

***Tusamitamab ravtansine (SAR408701)***

Tusamitamab ravtansine infusion will start after the end of pembrolizumab 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:**
  - Tusamitamab ravtansine 150 mg/m$^2$ (or 170 mg/m$^2$, or 120 mg/m$^2$, depending on the safety run-in DLTs and the Study Committee decision) or a lower dose (100 mg/m$^2$ or other, if applicable) will be administered via IV infusion over 1 hour 30 minutes on Day 1, and then Q3W. To prevent hypersensitivity reactions, premedication will be given before each administration (see below).
  - For participants with a body surface area (BSA) >2.20 m$^2$, the dose will be calculated based on a BSA of 2.20 m$^2$.

***Pemetrexed***

- **Formulation:** Refer to labeling for formulation of pemetrexed for injection.
- **Route of administration:** IV infusion.
- **Dose regimen:** Pemetrexed 500 mg/m$^2$ should be infused over 10 minutes after tusamitamab ravtansine infusion on Day 1 and then Q3W. All subjects should receive the appropriate supplementation of vitamin B12 and folic acid and corticosteroid prophylaxis.

***Cisplatin***

- **Formulation:** Refer to labeling for formulation of cisplatin for injection.
- **Route of administration:** IV infusion.
- **Dose regimen:** Cisplatin 75 mg/m$^2$ should be infused approximately 30 minutes after tusamitamab ravtansine (Part B) or pemetrexed (Part C) infusion on Day 1 and then Q3W for the first 4 cycles. Infusion of cisplatin should be immediately preceded and followed by hydration procedures and should be administered according to local practice and labels.

***Carboplatin***

- **Formulation:** Refer to labeling for formulation of carboplatin for injection.
- **Route of administration:** IV infusion.
- **Dose regimen:** Carboplatin AUC 5 mg/mL/min will be administered as an IV infusion over 15 to 60 minutes as per local practice and labels immediately after tusamitamab ravtansine (Part B) or pemetrexed (Part C) infusion on Day 1 and Q3W for the first 4 cycles. The carboplatin dose should not exceed 750 mg, and should be calculated using the Calvert formula and CrCl should be calculated by Cockcroft-Gault equation.

*Non-investigational medicinal products:*

***Premedication for tusamitamab ravtansine:***

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

Duration of study intervention

The expected duration of study intervention for participants may vary, based on disease progression date; median expected duration of study per participant is estimated at 10 months (up to 1 month for screening, a median of 6 months for treatment, a median of 1 month for EOT, and follow-up visit 90 days after the last IMP administration).

**Statistical considerations**

*Sample size calculations:*

- **Part A:**

  Assuming a prescreening failure rate of 80% (as per the initial protocol) and a study screening failure rate of 20%, approximately 38 to 388 participants would be prescreened to achieve 6 to approximately 62 participants (up to 12 DLT-evaluable participants at a DL other than the RDE in the Safety Run-In, at least 20 participants treated with the RDE [including participants at the RDE from the Safety Run-In], and a total of 20 to 30 participants treated at a lower DL (100 mg/m$^2$) or at an intermediate DL (120 mg/m$^2$). Assuming a prescreening failure rate of 45%, the number of participants could significantly be decreased (approximately 141 participants need to be prescreened to achieve 62 participants).

- **Part B:**

  Assuming a prescreening failure rate of 80% (as per the initial protocol), and a study screening failure rate of 20%, approximately 75 to 225 participants would be prescreened to achieve 12 to 36 DLT-evaluable participants in Part B. Assuming a prescreening failure rate of 45%, the number of participants to be prescreened could significantly be decreased (approximately 82 participants need to be prescreened to achieve 36 participants).

- **Part C:**

  Assuming a prescreening failure rate of 45% and a study screening failure rate of 20%, approximately 28 to 169 participants will be prescreened to achieve 12 to approximately 74 participants in Part C (up to 12 DLT-evaluable participants in each quadruplet combination arm treated at DL other than the RDE); overall regardless of the quadruplet

platinum combination arm, at least 20 participants treated with the RDE [including participants at the RDE from the Safety Run-In], and a total of 20 to 30 participants treated at a lower DL (100 mg/m$^2$) or at an intermediate DL (120 mg/m$^2$).

*Main analysis populations:*

- **All-treated population:**

  All participants assigned to study intervention and who have actually received at least 1 dose of study intervention.

- **DLT-evaluable population:**

  Participants who received 1 cycle with at least 80% of the intended dose for each IMP of the combination during the safety run-in of Part A, Part B or Part C. Participants should have completed Cycle 1 unless they experienced a DLT before the end of Cycle 1.

- **PK population:**

  All treated participants with at least 1 available concentration result postbaseline (whichever the cycle and even if dosing is incomplete) with adequate documentation of date and time of dosing and date and time of sampling.

- **ATA population:**

  All treated participants with at least 1 ATA result (negative, positive, or inconclusive) postbaseline.

*Analysis of primary endpoint:*

- The DLTs observed during the DLT observation period (Cycle 1) will be summarized on the DLT-evaluable population, by DL. 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.
- Objective response rate (ORR) will be summarized on the all-treated population by part, DL and overall using descriptive statistics and 95% exact confidence intervals (CIs) will be provided using the Clopper-Pearson method.

*Analysis of secondary efficacy endpoint:*

The secondary endpoints will be summarized by part, DL and overall.

- ORR (Part B) will be analyzed similarly as for Parts A & C.
- 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 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 premature discontinuation, TEAEs leading to permanent discontinuation, 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

**Figure 2 - Graphical study design for Part A**

Figure 2a : Study design for treatment in Part A

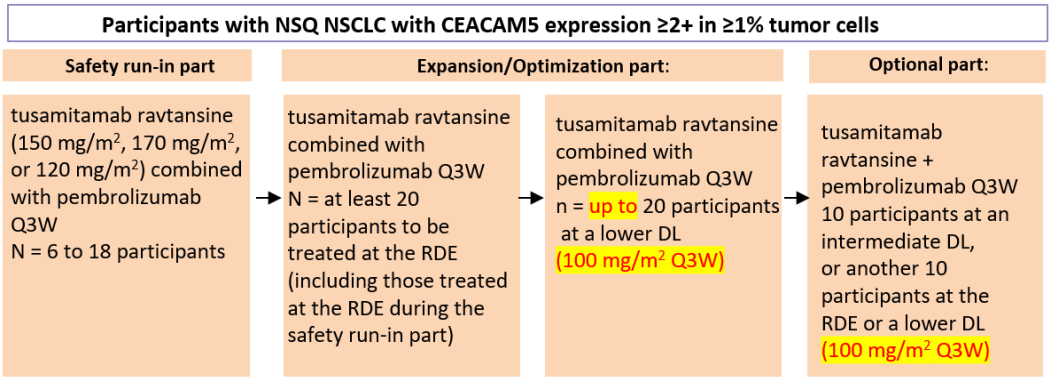
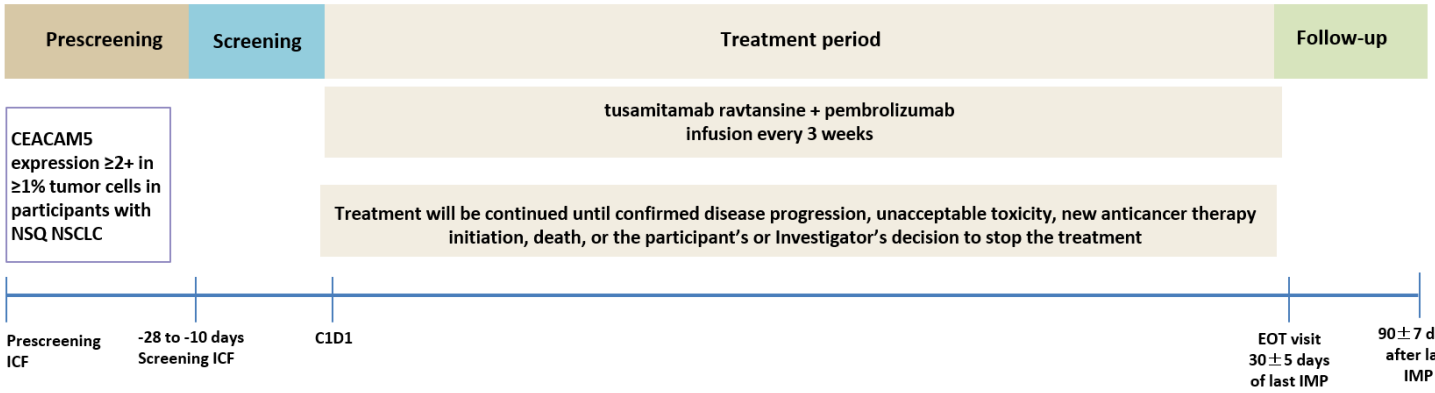
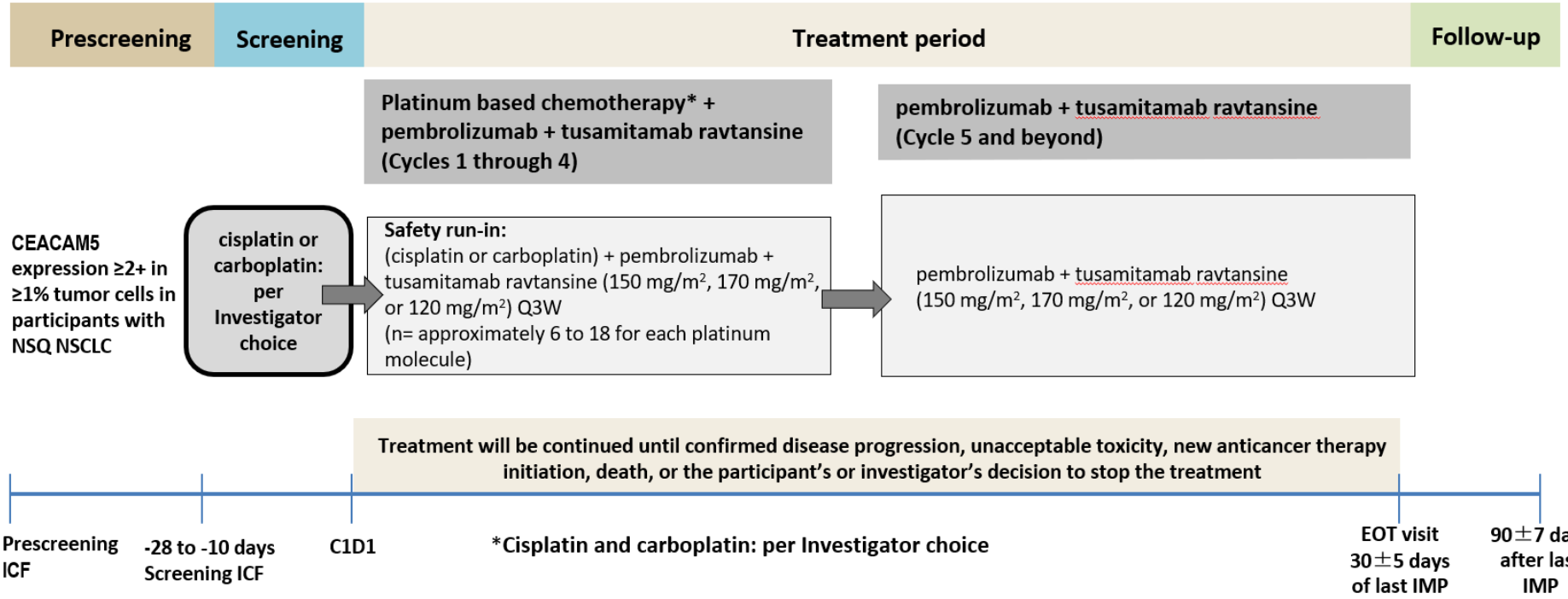



Figure 2b : Study design per participant for Part A




C: cycle; D: study day; CEACAM5: carcinoembryonic antigen-related cell adhesion molecule 5; DL: dose level; EOT: end of treatment; ICF: informed consent form; IMP: investigational medicinal product; NSQ NSCLC: nonsquamous non-small-cell lung cancer; RDE: recommend dose for expansion.

**Figure 3 - Graphical study design for Part B (Safety run-in only)**




C: cycle; CEACAM5: carcinoembryonic antigen-related cell adhesion molecule 5; D: study day; EOT: end of treatment; ICF: informed consent form; IMP: investigational medicinal product; NSQ NSCLC: nonsquamous, non-small-cell lung cancer

**Figure 4 - Graphical study design for Part C**

Figure 4a : Study design for treatment in Part C

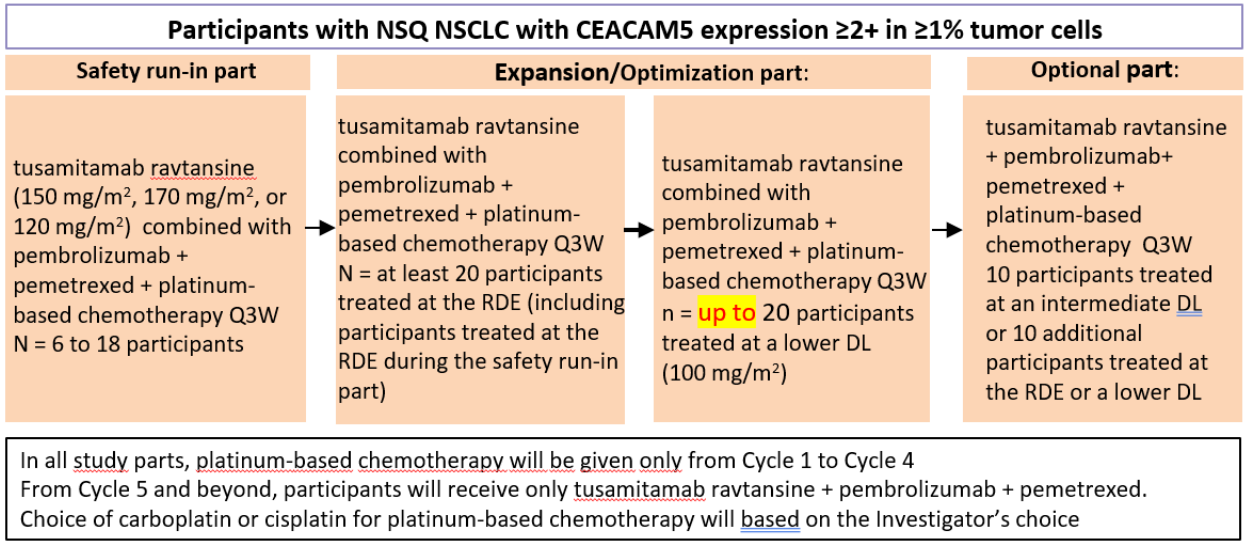
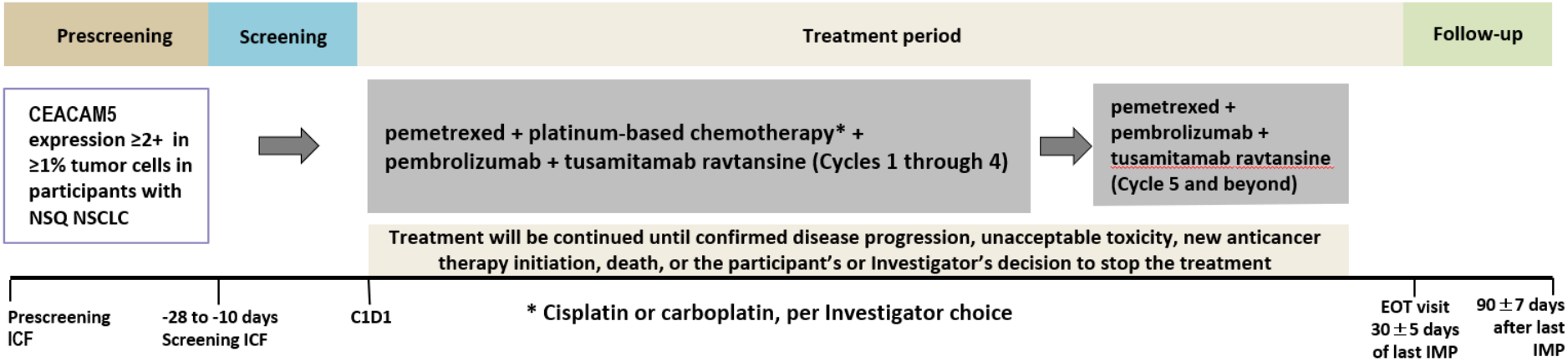



Figure 4b : Study design per participant for Part C




C: cycle; CEACAM5: carcinoembryonic antigen-related cell adhesion molecule 5; D: study day; EOT: end of treatment; ICF: informed consent form; IMP: investigational medicinal product; NSQ NSCLC: nonsquamous, non-small-cell lung cancer; RDE: recommended dose for expansion.

## 1.3 SCHEDULE OF ACTIVITIES (SOA)

### 1.3.1 Study procedures flowchart

| Procedure | Pre-screening[a] | Screening[b] | Treatment Cycle 1 | Treatment Cycle 2 and subsequent | | End of treatment | Follow-up visit[e] | Notes |
|---|---|---|---|---|---|---|---|---|
| **Day** | | **Days prior to initial infusion** | **D1 Pre-infusion[c]** | **D1 Pre-infusion[c] (±3 days)** | **Every 6 weeks (±7 days)** | **D30 after last infusion (±5 days)** | **90 days (±7 days)** | |
| CEACAM5 expression status[a] (archival or fresh tumor tissue) assessed by central IHC after prescreening informed consent. | X | | | | | | | |
| PD-L1 expression[a] (local assessment) | X | | | | | | | |
| Informed consent | | X[b] | | | | | | |
| IRT contact | X | X | X | X | | X | X | |
| Inclusion/exclusion criteria | | ≤28 | X | | | | | |
| Age | X | | | | | | | |
| Demography and medical/surgical/disease history/smoking history | | ≤28 | | | | | | |
| NSCLC characteristics | | ≤28 | | | | | | Includes histologic types, stage at diagnosis, disease extent at study entry |
| Height | | ≤7 | | | | | | |
| ECOG, Body Weight | | ≤7 | X | X | | X | | |
| Physical examination[f], signs and symptoms | | ≤7 | X | X | | X | X | |

| Procedure | Pre-screening[a] | Screening[b] | Treatment Cycle 1 | Treatment Cycle 2 and subsequent | | End of treatment | Follow-up visit[e] | Notes |
|---|---|---|---|---|---|---|---|---|
| **Day** | | **Days prior to initial infusion** | **D1 Pre-infusion[c]** | **D1 Pre-infusion[c] (±3 days)** | **Every 6 weeks (±7 days)** | **D30 after last infusion (±5 days)** | **90 days (±7 days)** | |
| Hematology[g] | | ≤7 | X (+weekly in C1) | X (+weekly in C2) | | X | | |
| Coagulation (INR) | | ≤7 | X | X | | X | | |
| Blood chemistry: liver function tests[h] | | ≤7 | X (+weekly in C1) | X (+weekly in C2) | | X | | |
| Blood chemistry: other tests[h] | | ≤7 | X | X | | X | | |
| Thyroid function | | ≤7 | | X | | X | | |
| HBsAg & HCV serology;<br>HIV test (only if required at country level) | | X | | | | | | |
| WOCBP: Urine or Serum pregnancy test[i] | | ≤7 | | X | | X | | Mandatory serum test at screening and EOT, serum or urine test during study treatment period. |
| 12-lead ECG | | ≤7 | | X | | X | | |
| Specific ocular tests[j] | | ≤28 | | | | X | | |
| Assessment of ocular/visual symptoms | | | X | X | | | | On the same day or within 2 days before each study intervention |
| **IMP administration[d]** | | | X | X | | | | |
| AE assessment | X[k] | X | Continuously throughout the study period | | | | | |
| Concomitant medication | | X | Continuously throughout the study period | | | | | |

| Procedure | Pre-screening[a] | Screening[b] | Treatment Cycle 1 | Treatment Cycle 2 and subsequent | | End of treatment | Follow-up visit[e] | Notes |
|---|---|---|---|---|---|---|---|---|
| Day | | Days prior to initial infusion | D1 Pre-infusion[c] | D1 Pre-infusion[c] (±3 days) | Every 6 weeks (±7 days) | D30 after last infusion (±5 days) | 90 days (±7 days) | |
| Tumor assessment - RECIST v1.1 - CT/MRI and surrogate markers when relevant (see Section 10.9 for details) | | ≤28 | | | X | X | | Baseline; every 6 weeks for the first 24 weeks; then every 9 weeks[e] |
| Circulating CEA[n] | X | ≤28 | | | X | X | | |
| FFPE sections for RNA and DNA analysis (archival or fresh tumor tissue)[o] | | X | X[p] | | | | | |
| Plasma for tumor cfDNA and whole blood for germline DNA | | | X | | | | | Additionally, plasma for tumor cfDNA isolation will be collected at pre-infusion of Cycle 5 Day 1. If the participant discontinues the treatment before Cycle 5, the sample can be taken at the end of treatment |
| Optional: whole blood for circulating tumoral cells (CTC)[l] | | | X | | | | | |
| IgG[m] | | | X | | | | | |
| Further anticancer therapy | | | | | | | X | |

| Procedure | Pre-screening[a] | Screening[b] | Treatment Cycle 1 | Treatment Cycle 2 and subsequent | | End of treatment | Follow-up visit[e] | Notes |
|---|---|---|---|---|---|---|---|---|
| Day | | Days prior to initial infusion | D1 Pre-infusion[c] | D1 Pre-infusion[c] (±3 days) | Every 6 weeks (±7 days) | D30 after last infusion (±5 days) | 90 days (±7 days) | |
| Tusamitamab ravtansine, pembrolizumab PK (Part A); tusamitamab ravtansine, pembrolizumab, carboplatin or cisplatin PK (Part B); tusamitamab ravtansine, pembrolizumab, pemetrexed, carboplatin or cisplatin PK (Part C) | | | See PK/ATA Flowchart in Section 1.3.2 | | | | | |
| Tusamitamab ravtansine Immunogenicity | | | See PK/ATA Flowchart in Section 1.3.2 | | | | | |

*a* **Prescreening:** a prescreening informed consent will be signed by the patient before CEACAM5 assay on archival or fresh tumor tissue. Patients who have additional tumor tissue samples available during the prescreening phase may be re-assessed for CEACAM5 expression level and the most recent tissue sample assessed for CEACAM5 expression will be used to determine eligibility of patients for screening. Participants will require local or central assessment of tumor PD-L1 expression. Circulating CEA will be performed locally if possible.

*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. Routine baseline tests performed prior to ICF signature do not need to be repeated as long as they are within the screening defined timeframe. 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-positive expression as assessed centrally. Baseline evaluation should be completed within 1 week prior to initiation of therapy, except for tumor assessment, circulating CEA, and ocular tests that may be performed within 4 weeks prior to the first IMP administration. Results of these tests should be reviewed by the Investigator prior to initiation of therapy.

*c* **D1 predose**: 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 and coagulation tests may be omitted if baseline test performed within 7 days are normal. If baseline tests are abnormal, they should be repeated within 2 days of first study intervention.

*d* **Treatment**: participants should receive study intervention until confirmed disease progression, unacceptable toxicity, new anticancer therapy initiation, death, or the participant's or investigator's decision to stop the treatment.

*e* **Follow-up visit:** at the follow-up visit, SAEs/AESIs (regardless of relationship with study treatment) and IMP-related AEs ongoing at the end of study treatment, and any new IMP-related AE/SAE/AESI will be followed until resolution or stabilization (stabilization is defined as an event ongoing without any change for at least 3 months). Date of disease progression (PD) and further anticancer treatment will be collected at the follow-up visit. Tumor assessments are performed at baseline, every 6 weeks for the first 24 weeks from C1D1, and thereafter every 9 weeks until radiological disease progression, death, study cut-off date of the secondary endpoints, initiation of further anticancer therapy, or withdrawal of participant's consent, whichever comes first. A participant who stops treatment before documented progressive disease should undergo tumor assessments as for those who continued treatment up to PD.

*f* **Physical examination** will include: vital signs (temperature, blood pressure, pulse rate) and examination of major body systems including cardiovascular, central nervous system, respiratory system, hepatomegaly, splenomegaly, lymphadenopathy. Signs and symptoms will be reported in the eCRF as AEs only if they are still present at the time of first IMP administration.

*g* **Hematology**: Hemoglobin, hematocrit, WBC with differential, platelet counts. If Grade 4 neutropenia, assess ANC every 2-3 days until ANC ≥0.5 x $10^9$/L.

*h* **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, phosphate, chloride, Others: Glucose, LDH, albumin and total proteins. The liver function tests and renal function tests will be done before IMP administration at each cycle. In case of Grade ≥3 liver function abnormal tests, additional tests will be repeated every 2-3 days until recovery to baseline value.

*i* **Serum pregnancy test**: WOCBP must have a negative serum pregnancy test result within 7 days prior to the initial dose of IMP. A pregnancy test (urine or serum as required by local regulations) will be repeated every 3 weeks before each IMP administration and at the end of treatment evaluation.

*j* **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, EOT and whenever clinically indicated.

*k* **AEs/SAEs during the prescreening period:** only AEs/SAEs related to the fresh biopsy procedure (if applicable) and occurring within 1 month after the fresh biopsy will be recorded in the eCRF.

*l* A sample for **CTC analysis** will be taken in a maximum of 10 participants during the course of the study.

*m* Sampling for IgG may be stopped during the course of the study, upon notification from the Sponsor

*n* For CEA sample collection scheduled on the day of a treatment visit, samples should be drawn prior to initiation of any IMP infusion

*o* At least 3 × 10 µm slides (best) or 6 × 3–5 µm slides (or equivalent to the same total amount of material) from FFPE tissue (from same sample as the one used for CEACAM5 expression status if possible) is requested at screening or C1D1, if enough material is available. An additional 5 µm section is requested for hematoxyline-eosine staining.

*p* If FFPE sections for RNA and DNA analysis not performed at Screening, then back-up could be at C1D1.

AE: adverse event; AESI: adverse event of special interest; ALT: alanine aminotransferase; ANC: absolute neutrophil count; AP: alkaline phosphatase; AST: aspartate aminotransferase; ATA: antitherapeutic antibody; BUN: blood urea nitrogen; C: Cycle; CEA: carcinoembryonic antigen; CEACAM5: carcinoembryonic antigen-related cell adhesion molecule 5; cfDNA: circulating free deoxyribonucleic acid; CT: computed tomography; D: Day; DNA: deoxyribonucleic acid; ECG: electrocardiogram; eCRF: electronic caser report form; EOT: end of treatment; FFPE: formalin-fixed, paraffin embedded; HBsAg: hepatitis B surface antigen; HCV: hepatitis C virus; HIV: human immunodeficiency virus; IHC: immunohistochemistry; IMP: investigational medicinal product; INR: international normalized ratio; IRT: interactive response technology; LDH: lactate dehydrogenase; MRI: magnetic resonance imaging; NSCLC: non-small-cell lung cancer; PD-1: programmed cell death protein 1; PD-L1: programmed death-ligand 1; PK: pharmacokinetic; PS: performance status; RECIST: response evaluation criteria in solid tumors; SAE: serious adverse event; SGOT: serum glutamic-oxaloacetic transaminase; SGPT: serum glutamic-pyruvic transaminase; TA: tumor assessment; VS: vital signs; WBC: white blood cell; WOCBP: woman of childbearing potential.

## 1.3.2 PK/ATA flowchart

### *1.3.2.1 PK/ATA flow chart for Part A*

| Cycle | | C1 | | | C2 | C3 | C4 | | C5 and beyond[b, c, d] | EOT |
|---|---|---|---|---|---|---|---|---|---|---|
| Day | | D1 | | D4 | D1 | D1 | D1 | | D1 | D30 ±5 days after last IMP |
| Pembrolizumab | IV infusion | X--- | | | X | X | X | | X | |
| | Sample RNT (hours) Ref. Pembrolizumab SOI | SOI | | | SOI | | SOI | | SOI | |
| | Sample time window | (-24 h, SOI) | | | (-24 h, SOI) | | (-24 h, SOI) | | (-24 h, SOI) | |
| | PK sample ID | 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+1 h | SOI | |
| | Sample time window | (-24 h, SOI) | ±10 min | ±24 h | (-24 h, SOI) | (-24 h, SOI) | (-24 h, SOI) | ±10 min | (-24 h, SOI) | |
| | PK sample ID (SAR408701, DM4 and Me-DM4[f]) | P00[a] | P01[e] | P02 | P00[a] | P00[a] | P00[a] | P01 | P00[a, c] | |
| | ATA sample ID | AB00[a] | | | AB00[a] | AB00[a] | AB00[a] | | AB00[a, d] | ABF00 |

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

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

*b* Pembrolizumab PK samples will be collected at SOI at Cycle 8 only.

*c* Tusamitamab ravtansine PK samples will be collected at SOI each cycle at Cycles 5, 6, 7, and 8; thereafter, only at Cycle 13.

*d* Tusamitamab ravtansine ATA samples will be collected at SOI at Cycle 6, Cycle 8 and thereafter every 5 cycles (ie, C8, C13, C18…).

*e* Actual EOI sample should be taken when the pump beeps (end of infusion) before flush.

*f* DM4 and Me-DM4 to be collected only for participants enrolled from amendment #6

ATA: antitherapeutic 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.

### *1.3.2.2 PK/ATA flow chart for Part B*

| Cycle | | C1 | | | | | C2 | C3 | C4 | | C5 and beyond[b, c, d] | EOT |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Day | | D1 | | | | D4 | D1 | D1 | D1 | | D1 | D30 ±5 days after last IMP |
| Pembrolizumab | IV infusion | X--- | | | | | X | X | X | | X | |
| | Sample RNT (hours)<br>Ref. Pembrolizumab SOI | SOI | | | | | SOI | | SOI | | SOI | |
| | Sample time window | (-24 h, SOI) | | | | | (-24 h, SOI) | | (-24 h, SOI) | | (-24 h, SOI) | |
| | PK sample ID | S00[a] | | | | | S00[a] | | S00[a] | | S00[a, b] | |
| Tusamitamab ravtansine | IV infusion | X--- | ---X | | | | X | X | X | | X | |
| | Sample RNT (hours)<br>Ref. tusamitamab ravtansine SOI | SOI | EOI | | | 72h | SOI | SOI | SOI | EOI+1 h | SOI | |
| | Sample time window | (-24 h, SOI) | ±10 min | | | ±24 h | (-24 h, SOI) | (-24 h, SOI) | (-24 h, SOI) | ±10 min | (-24 h, SOI) | |
| | PK sample ID<br>(SAR408701, DM4 and Me-DM4[f]) | P00[a] | P01[e] | | | P02 | P00[a] | P00[a] | P00[a] | P01 | P00[a, c] | |
| | ATA sample ID | AB00[a] | | | | | AB00[a] | AB00[a] | AB00[a] | | AB00[a, d] | ABF00 |
| Cisplatin/Carboplatin | IV infusion | X--- | ---X | | | | | | | | | |
| | Sample RNT (hours)<br>Ref. cisplatin/carboplatin SOI | SOI | EOI | EOI+1H | Cisplatin: EOI+3H<br>Carboplatin: EOI+4H | | | | | | | |
| | Sample time window | (-24 h, SOI) | Within 5 min before EOI | ±10 min | ±15 min | | | | | | | |
| | PK sample ID | P00[a] | P01 | P02 | P03 | | | | | | | |

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

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

*b* Pembrolizumab PK samples will be collected at SOI at Cycle 8 only.

*c* Tusamitamab ravtansine PK samples will be collected at SOI each cycle at Cycles 5, 6, 7, and 8; thereafter, only at Cycle 13.

*d* Tusamitamab ravtansine ATA samples will be collected at SOI at Cycle 6, Cycle 8 and thereafter every 5 cycles (ie, C8, C13, C18).

*e* Actual EOI sample should be taken when the pump beeps (end of infusion) before flush.

*f* DM4 and Me-DM4 to be collected only for patients enrolled from amendment #6

ATA: antitherapeutic 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.

### *1.3.2.3 PK/ATA flow chart for Part C*

| Cycle | | C1 | | | | | | | C2 | C3 | C4 | | C5 and beyond[b, c, d] | EOT |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Day | | D1 | | | | | D2 | D4 | D1 | D1 | D1 | | D1 | D30 ±5 days after last IMP |
| Pembrolizumab | IV infusion | X--- | | | | | | | X | X | X | | X | |
| | Sample RNT (hours) Ref. Pembrolizumab SOI | SOI | | | | | | | SOI | | SOI | | SOI | |
| | Sample time window | (-24 h, SOI) | | | | | | | (-24 h, SOI) | | (-24 h, SOI) | | (-24 h, SOI) | |
| | PK sample ID | 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+1 h | SOI | |
| | Sample time window | (-24 h, SOI) | ±10 min | | | | | ±24 h | (-24 h, SOI) | (-24 h, SOI) | (-24 h, SOI) | ±10 min | (-24 h, SOI) | |
| | PK sample ID (SAR408701, DM4 and Me-DM4[f]) | P00[a] | P01[e] | | | | | P02 | P00[a] | P00[a] | P00[a] | P01 | P00[a, c] | |
| | ATA sample ID | AB00[a] | | | | | | | AB00[a] | AB00[a] | AB00[a] | | AB00[a, d] | ABF00 |
| Pemetrexed | IV infusion | X | | | | | | | | | | | | |
| | Sample RNT (hours) Ref. pemetrexed SOI | SOI | 30 min | 2h | 4h | 8h | 24h | | | | | | | |
| | Sample time window | (-24 h, SOI) | ±10 min | ±15 min | ±30 min | ±1 h 30 | ±5 h | | | | | | | |
| | PK sample ID | P00[a] | P01 | P02 | P03 | P04 | P05 | | | | | | | |

| Cycle | | C1 | | | | | | | C2 | C3 | C4 | | C5 and beyond[b, c, d] | EOT |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Day | | D1 | | | | | D2 | D4 | D1 | D1 | D1 | | D1 | D30 ±5 days after last IMP |
| Cisplatin/Carboplatin | IV infusion | X--- | ---X | | | | | | | | | | | |
| | Sample RNT (hours) Ref. cisplatin/ carboplatin SOI | SOI | EOI | EOI+1H | Cisplatin: EOI+3H Carboplatin: EOI+4H | | | | | | | | | |
| | Sample time window | (-24 h, SOI) | Within 5 min before EOI | ±10 min | ±15 min | | | | | | | | | |
| | PK sample ID | P00[a] | P01 | P02 | P03 | | | | | | | | | |

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

*a* Samples collected strictly before start of infusion (SOI), tusamitamab ravtansine, pembrolizumab, pemetrexed and cisplatin or carboplatin predose samples can be collected at the same time before pembrolizumab administration.

*b* Pembrolizumab PK samples will be collected at SOI at Cycle 8 only.

*c* Tusamitamab ravtansine PK samples will be collected at SOI each cycle at Cycles 5, 6, 7, and 8; thereafter, only at Cycle 13.

*d* Tusamitamab ravtansine ATA samples will be collected at SOI at Cycle 6, Cycle 8 and thereafter every 5 cycles (ie, C8, C13, C18…).

*e* Actual EOI sample should be taken when the pump beeps (end of infusion) before flush.

*f* DM4 and Me-DM4 to be collected only for patients enrolled from amendment #6

ATA: antitherapeutic 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.

# 2 INTRODUCTION

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, a tumor-associated carcinoembryonic antigen, 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.

Carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5) was 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.

## 2.1 STUDY RATIONALE

The management of patients with metastatic NSCLC underwent significant transformation in the last 10-15 years with the development of precision medicine based on molecular characterization. Molecular analysis revealed distinct targetable driver mutations in about 10% to 20% of patients with metastatic NSCLC. In Asia, the prevalence is even 30% to 40%.

Tusamitamab ravtansine ADC has shown a significant level of activity and a favorable safety profile in heavily pretreated NSQ metastatic NSCLC patients. Study TED13751 included a cohort of patients with heavily pretreated, NSQ NSCLC tumors treated with tusamitamab ravtansine 100 mg/m² Q2W. In the 64 treated patients with ≥50% CEACAM5 expression, tusamitamab ravtansine showed encouraging antitumor activity associated with an overall response rate of 20.3% per RECIST1.1 (95% CI: 12.27%-31.71%), warranting further development of tusamitamab ravtansine to treat this patient population. In the 28 treated patients with NSQ NSCLC CEACAM5 expression ≥1% and <50%, the overall response rate was 7.1% per RECIST◦1.1 (95% CI: 1.98%-22.65%).

Besides these 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 (June 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 3 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).

Pembrolizumab in combination with chemotherapy is also 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 (6). Improvement in OS was seen across all PD-L1 categories that were evaluated. Median PFS 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 should improve the outcome, with a better tolerability for doublet or triplet combinations, and without additional toxicity for the quadruplet combination, as no overlapping toxicities are expected.

Encouraging preliminary efficacy data, from ongoing ACT16146 study, have been observed in the first 25 patients treated in the study. The results observed in TED13751 where tusamitamab ravtansine was administered as monotherapy at 100 mg/m² Q2W in patients with CEACAM5 expression ≥1% and these preliminary efficacy data from Part A where tusamitamab ravtansine is administered in combination with pembrolizumab in patients with CEACAM5 expression ≥50% open the door to a decrease in threshold of CEACAM5 expression from 50% to 1%.

The objective of this study is to evaluate the safety and antitumor activity efficacy of tusamitamab ravtansine in combination with pembrolizumab, tusamitamab ravtansine in combination with pembrolizumab and platinum-based chemotherapy (Investigator's choice of cisplatin or carboplatin) and tusamitamab ravtansine in combination with the standard of care for first-line treatment pembrolizumab, platinum-based chemotherapy (Investigator's choice of cisplatin or carboplatin) and pemetrexed in untreated advanced/metastatic NSQ NSCLC participants with CEACAM5 high or moderate expression (high expression is defined as CEACAM5 immunohistochemistry [IHC] intensity ≥2+ in ≥50% of tumor cells and moderate expression is defined as intensity ≥2+ in ≥1% and <50% of tumor cells) in tumors.

## 2.2 BACKGROUND

Lung cancer is one of the most commonly diagnosed cancers and is the leading cause of cancer-related mortality worldwide (7). Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancers and comprises several histopathological subtypes, the most common of which are adenocarcinoma (40% to 60%) and squamous cell carcinoma (10% to 15%) (8).

The majority of NSCLC patients presents with an advanced stage of disease at the time of diagnosis. These patients have a median OS of up to 8 to 12 months, and a 5 year survival rate of approximately 18% (8). Between 10% and 20% of patients with NSCLC have tumors with key genomic alterations that are amenable to targeted therapy, which include EGFR mutations and ROS1 and ALK rearrangements.

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 (9).

More recently, immunotherapy has initiated a new paradigm for the treatment of NSCLC. In particular, monoclonal antibodies targeting the PD-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 (10, 11, 12, 13), however only a few patients (20% to 30%) respond 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 in patients with advanced/metastatic NSCLC.

Tusamitamab ravtansine is being investigated in ongoing trials including 4 studies enrolling participants with NSCLC:

- First-in-human (FIH) Study TED13751 to evaluate safety, PK, and antitumor activity of tusamitamab ravtansine in patients with advanced solid tumors.
- Phase 3 trial EFC15858, a randomized, open-label, multicenter study comparing tusamitamab ravtansine and docetaxel in patients with metastatic NSQ NSCLC expressing CEACAM5 and previously treated with platinum-based chemotherapy and an ICI, if indicated.
- Phase 2 trial ACT16525, an open-label, single-arm trial to evaluate antitumor activity, safety, and pharmacokinetics of tusamitamab ravtansine used in combination with ramucirumab in metastatic NSQ NSCLC patients with CEACAM5-positive tumors, previously treated with platinum-based chemotherapy and an ICI.
- Phase 2 trial ACT17241, an open-label trial evaluating the efficacy and safety of tusamitamab ravtansine in participants with NSQ NSCLC who have tumors with negative or moderate CEACAM5 expression and high circulating CEA.

## 2.3 BENEFIT/RISK ASSESSMENT

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

More detailed information about the known and expected benefits and risks and reasonably expected AEs of tusamitamab ravtansine may be found in the Investigator's brochure (IB). Details regarding important identified risks and expected benefits for pembrolizumab can be found in the Product Information.

### 2.3.1 Risk assessment

In the completed main escalation phase of TED13751, 31 patients have been treated across 8 DLs ranging from 5 to 150 mg/m².

Treatment-emergent adverse events (TEAEs) were seen in 29 of 31 patients in the main dose escalation, 54.8% patients experienced a Grade 3 or higher TEAE and 41.9% patients had at least 1 serious TEAE. Grade ≥3 TEAEs related to tusamitamab ravtansine were seen in 7 patients (22.6%), and were reported as SAEs in 2 patients (6.5%). One patient experienced the Grade 4 events of neutropenia and colitis erosive, and 1 patient experienced the Grade 1 event of colitis. The most frequent (in ≥4 of 31 patients [≥12.9%]) all-cause TEAE PTs were asthenia, nausea, and decreased appetite (8 patients [25.8%] each); keratopathy (8 patients [25.8%] any grade; 6 patients [19.4%] Grade ≥3); diarrhea and constipation (7 patients [22.6%] each); diarrhea/colitis combined (9 patients [29%]); fatigue (6 patients [19.4%]); abdominal pain (5 patients [16.1%]); dry eye and xerophthalmia combined (7 patients [22.6%]); and blurred vision and cough (4 patients [12.9%] each). Nervous system disorders occurred in 8 patients; these included paresthesia in 4 patients (12.9%), peripheral sensory neuropathy in 2 patients (6.5%), neuropathy in 1 patient (3.3%), and dysesthesia in 1 patient (3.3%). Infectious conditions, which included 3 Grade ≥3 events, were observed in 5 patients (16.1%). Except for keratopathy, these events were predominantly of low severity (Grade 1/Grade 2). The main clinically relevant laboratory abnormality was thrombocytopenia (51.6% [versus 9.7% at baseline]). Neutropenia has been observed in 5 patients (16.1%); 3 had Grade >3 events. Events possibly linked to allergic processes were documented in 2 patients (1 patient with Grade 2 infusion reaction, and 1 patient with Grade 1 eczematous lesions).

During the assessment of preliminary safety data as a data extraction from ongoing expansion cohorts, among 114 patients treated at 100 mg/m² tusamitamab ravtansine and treated with right-eye prophylaxis in the expansion phase, a TEAE of the cornea was reported in 31 patients; 29 patients had clear laterality assessment. Preliminary results showed that about 93% of corneal events (27 of 29 events) were bilateral, and thus were not impacted by prophylactic treatment. Based on this preliminary result, it has been decided to discontinue primary ocular prophylaxis, and instead consider secondary prophylaxis on a case-by-case basis following an ophthalmologist's recommendation based on assessment of an individual patient.

In Study TCD15054 to evaluate safety and PK of tusamitamab ravtansine monotherapy in Japanese patients, TEAEs have been reported in 8 patients (88.9%) and 2 (22.2%) of them were reported as Grade ≥3 events. TEAEs related to tusamitamab ravtansine were reported in 6 patients (66.7%); only 1 patient (11.1%) had Grade ≥3 event (Gastrointestinal hemorrhage). One patient permanently discontinued study treatment due to an AE (Grade 1 blurred vision event).

To date, efficacy and safety data from ongoing studies of tusamitamab ravtansine (TED13751 and TCD15054) support continued clinical development. Based on available safety data, the main anticipated risk to participants is corneal toxicity presenting as keratitis/microcystic keratopathy, which is reversible and manageable with dose delay and dose reduction in some participants. Peripheral neuropathy is an identified risk in participants previously exposed to neurotoxic drugs. Other potential risks include colitis (including hemorrhagic), bone marrow toxicity, cardiotoxicity (myocardial or conduction abnormalities) and increases in liver enzymes, as well as systemic acute hypersensitivity reactions (including anaphylaxis and local infusion site reaction to tusamitamab ravtansine). More detailed information about the known and expected benefits and risks and reasonably expected AEs of tusamitamab ravtansine may be found in the current Investigator's Brochure.

Pembrolizumab is most commonly associated with immune-related adverse reactions. The safety of pembrolizumab as monotherapy has been evaluated in 5,884 patients with advanced melanoma, resected Stage III melanoma (adjuvant therapy), NSCLC, classical Hodgkin's lymphoma, urothelial carcinoma, or head and neck squamous-cell carcinoma (HNSCC) across 4 doses (2 mg/kg Q3W, 200 mg Q3W, or 10 mg/kg every 2 or 3weeks) in clinical studies. The most frequent adverse reactions with pembrolizumab were fatigue (32%), nausea (20%), and diarrhea (20%). The majority of adverse reactions reported for monotherapy were of Grade 1 or 2 severity. The most serious adverse reactions were immune-related adverse reactions and severe infusion-related reactions.

The safety of pembrolizumab in combination with chemotherapy (pemetrexed and platinum) has been evaluated in 1 067 patients with NSCLC or HNSCC receiving 200 mg, 2 mg/kg, or 10 mg/kg pembrolizumab Q3W in clinical studies. In this patient population, the most frequent adverse reactions were nausea (50%), anemia (50%), fatigue (37%), constipation (35%), diarrhea (30%), neutropenia (30%), decreased appetite (28%), and vomiting (25%). Incidences of Grade 3-5 adverse reactions were 67% for pembrolizumab combination therapy and 66% for chemotherapy alone. In general, the frequency of adverse reactions from treatment with pembrolizumab in combination is higher than for pembrolizumab as monotherapy or for chemotherapy alone, reflecting the contribution of each of these components.

Given the significant risks of AEs associated with pembrolizumab (see US Package Insert or EU Summary of Product Characteristics for Keytruda or the EU Summary of risk management plan for pembrolizumab), and AEs associated with platinum-based chemotherapy, a specific interest will be given to closely monitor the safety profile of the combination of tusamitamab ravtansine and pembrolizumab with or without platinum-based chemotherapy.

Commonly reported AEs of pemetrexed include nausea, vomiting, loss of appetite, diarrhea, stomach upset, changes in taste, constipation, mouth sores, and tiredness, of which nausea, vomiting, and diarrhea can be severe. Common side effects of platinum-based chemotherapy include anaphylaxis, cytopenia (including leukopenia and neutropenia, thrombocytopenia, and anemia), hepatotoxicity, ototoxicity, cardiotoxicity, nausea and vomiting, diarrhea, mucositis, stomatitis, pain, alopecia, anorexia, cachexia, and asthenia. Identified dose-limiting toxicities include nephrotoxicity for cisplatin, myelosuppression for carboplatin, and neurotoxicity for oxaliplatin.

Given the considerable toxicity associated with pemetrexed and/or platinum chemotherapies, the combination of tusamitamab ravtansine with pembrolizumab and with or without platinum-based chemotherapy should lead to improved outcomes, as compared to a combination with untargeted, toxic chemotherapy. As hematological toxicity is minimal for tusamitamab ravtansine, its combination with the standard of care may lead to better efficacy with acceptable safety profile.

### 2.3.2 Benefit assessment

Based on the current data obtained in the ongoing monotherapy studies of tusamitamab ravtansine (TED13751 and TCD15054), the perceived balance between the anticipated benefits and the reported risks of tusamitamab ravtansine with advanced malignancies is acceptable and supports continued clinical development of the agent, including in combination with chemotherapy and immunotherapy agents.

As of 28 Nov 2022, preliminary efficacy analysis of data was performed on the 25 participants treated in the 3 combination treatment cohorts with encouraging data.

### 2.3.3 Overall benefit: risk conclusion

Taking into account the measures taken to minimize risk to participants, the potential risks identified in association with tusamitamab ravtansine combined with pembrolizumab with or without platinum-based chemotherapy and with or without pemetrexed are justified by the anticipated benefits that may be afforded to participants with advanced/metastatic NSCLC.

# 3 OBJECTIVES AND ENDPOINTS

**Table 1 - Objectives and endpoints**

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • Safety run-in part: to assess the tolerability and to determine the recommended doses of tusamitamab ravtansine in combination with pembrolizumab and tusamitamab ravtansine in combination with pembrolizumab and platinum-based chemotherapy with or without pemetrexed to be tested in the expansion part of the study in the NSQ NSCLC population | • Incidence of study drug-related dose-limiting toxicity (DLTs) at Cycle 1 (C1D1 to C1D21), including but not limited to corneal toxicity |
| • Expansion part (including participants treated at the recommended dose for expansion [RDE] from the Safety Run-in part): to assess the antitumor activity of several dose levels (DLs; if applicable) of tusamitamab ravtansine in combination with pembrolizumab and of several DLs of tusamitamab ravtansine in combination with pembrolizumab, platinum-based chemotherapy, and pemetrexed in the NSQ NSCLC population | • Objective response rate (ORR) defined as proportion of participants who have a confirmed complete response (CR) or partial response (PR) as per best overall response RECIST v1.1 (2) |
| **Secondary** | |
| • To assess the safety and tolerability of several DLs (if applicable) of tusamitamab ravtansine in combination with pembrolizumab and of 1 DL of tusamitamab ravtansine in combination with pembrolizumab and platinum-based chemotherapy, and of several DLs of tusamitamab ravtansine in combination with pembrolizumab and platinum-based chemotherapy with pemetrexed in the NSQ NSCLC population. | • Incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs) and laboratory abnormalities according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) V5.0 |
| • To assess the antitumor activity of several DLs (if applicable) of tusamitamab ravtansine in combination with pembrolizumab and of 1 DL of tusamitamab ravtansine in combination with pembrolizumab and platinum-based chemotherapy, and of several DLs of tusamitamab ravtansine in combination with pembrolizumab, and platinum-based chemotherapy, with pemetrexed in the NSQ NSCLC population | • Progression-free survival (PFS), 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 (not for Part B)<br>• Disease control rate (DCR), defined as the percentage of participants who have achieved confirmed CR, confirmed PR or stable disease as best overall response per RECIST v1.1 |
| • To assess the durability of the response to treatment with several DLs (if applicable) of tusamitamab ravtansine in combination with pembrolizumab and of 1 DL of tusamitamab ravtansine in combination with pembrolizumab and platinum-based chemotherapy, and of several DLs of tusamitamab ravtansine in combination with pembrolizumab,platinum-based chemotherapy, and pemetrexed in the NSQ NSCLC population. | • 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 |

| Objectives | Endpoints |
|---|---|
| • To assess the antitumor activity of tusamitamab ravtansine in combination with pembrolizumab and platinum-based chemotherapy in the NSQ NSCLC population | • Objective response rate defined as proportion of participants who have a confirmed complete response (CR) or partial response (PR) as per BOR per RECIST v1.1 (2) |
| • To assess the pharmacokinetics (PK) of tusamitamab ravtansine, pembrolizumab, pemetrexed, cisplatin, and carboplatin, each when given in combination as a doublet (tusamitamab ravtansine + pembrolizumab) or triplet (tusamitamab ravtansine + pembrolizumab + platinum-based chemotherapy) or a quadruplet (tusamitamab ravtansine + pembrolizumab + platinum-based chemotherapy + pemetrexed) | • Pharmacokinetic concentrations of tusamitamab ravtansine (SAR408701, DM4, Me-DM4), pembrolizumab, pemetrexed, cisplatin, and carboplatin |
| • To assess the immunogenicity of tusamitamab ravtansine in combination with pembrolizumab and tusamitamab ravtansine in combination with pembrolizumab and platinum-based chemotherapy with or without pemetrexed | • Incidence of antitherapeutic antibodies (ATAs) against tusamitamab ravtansine |
| **Tertiary/Exploratory** | |
| • To explore modulations of circulating carcinoembryonic antigen (CEA) as a potential pharmacodynamic (PD) biomarker of response to tusamitamab ravtansine treatment and to evaluate circulating CEA levels at prescreening | • Circulating CEA at prescreening, screening, and during the treatment period |
| • To explore the relationship between the tumor mutation profiles detected in the circulating free deoxyribonucleic acid (cfDNA) at baseline with efficacy outcome and to explore decrease in cfDNA in response to treatment | • Plasma analysis for tumor cfDNA at baseline and Cycle 5 |
| • To explore CEACAM5 expression on circulating tumoral cells (CTCs) | • CEACAM5 expression assessment on CTCs from patients with positive (high) CEACAM5 expression on tumor tissue |
| • To explore potential sets of biomarkers from tumor DNA and RNA analyses, beside target expression, as potential biomarkers of response to treatment | • Biomarker annotation for tumor DNA and RNA at baseline |
| • To explore PK-PD relationships | • Relationship between tusamitamab ravtansine PK exposure and safety endpoints of interest may be investigated as well as between tusamitamab ravtansine PK and efficacy endpoints (eg, ORR) |

## 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, multicenter study which will comprise 3 parts: Part A, Part B, and Part C. Part A is to assess safety, efficacy (antitumor activity), and PK of the tusamitamab ravtansine combined with pembrolizumab in NSQ NSCLC participants with CEACAM5 high or moderate expression (high expression is defined as CEACAM5 IHC intensity ≥2+ in ≥50% of tumor cells or moderate expression as intensity ≥2+ in ≥1% and <50% of tumor cells). Part B is to assess safety, efficacy (antitumor activity), and PK of the tusamitamab ravtansine combined with pembrolizumab and platinum-based chemotherapy in NSQ NSCLC participants with CEACAM5 high or moderate expression tumors. Part C is to assess safety, efficacy (antitumor activity), and PK of the tusamitamab ravtansine combined with pembrolizumab, platinum-based chemotherapy and pemetrexed in NSQ NSCLC participants with CEACAM5 high or moderate expression tumors. A safety run-in phase will be conducted for each part of the study to define the recommended doses of tusamitamab ravtansine in a combination regimen with pembrolizumab for the expansion part. An expansion part consisting of the evaluation of the antitumor activity, safety, and PK of tusamitamab ravtansine at 2 or 3 DLs combined with pembrolizumab will be performed in Part A and C to further evaluate the efficacy, safety, and PK of tusamitamab ravtansine to determine the recommended tusamitamab ravtansine DL for evaluation in Phase 3 studies.

During the prescreening phase, patients' tumor samples will be collected to evaluate CEACAM5 status (central assessment by IHC); PD-L1 status by an approved test will be collected and assessed locally or centrally, and circulating CEA will be assessed locally.

During the screening phase, participants with NSQ NSCLC determined to be CEACAM5 high expression (≥50%) or moderate expression (≥1% and <50%) tumors will go through protocol screening procedures and be enrolled in Part A, Part B or Part C per Investigator's choice.

### 4.1.1 Safety run-in part: DLT observation period

In Parts A, B and C, the DLT observation period is the first cycle (21 days). Depending on the DLTs observed, up to 3 DLs of tusamitamab ravtansine can be tested: 150 mg/m², 170 mg/m², and 120 mg/m².

For each DL of each combination arm, a minimum of 1 week is mandatory between the first dose of the first participant treated at this DL and the first dose of the next participant treated at the same DL. Once 3 participants assigned to a combination arm have been treated at a DL and are DLT-evaluable, the tolerability of the combination is assessed according to the decision algorithm as illustrated in Figure 1.

**PART A:**

The tolerability and safety of the pembrolizumab and tusamitamab ravtansine combination will be assessed. The first 3 participants will receive Q3W a 200 mg pembrolizumab infusion followed by a tusamitamab ravtansine infusion at the starting dose of 150 mg/m². The rules to determine the recommended doses for expansion are detailed in Section 6.6.1.

The tolerability of the doublet combination will be assessed in approximately 6 to 18 participants to determine the RDE.

**PART B:**

The tolerability and safety of the pembrolizumab, tusamitamab ravtansine, and platinum-based chemotherapy combination will be assessed. Participants can be assigned to either cisplatin or carboplatin per Investigator choice.

- **Cisplatin combination arm:** participants will receive Q3W pembrolizumab 200 mg + tusamitamab ravtansine (150 mg/m², 170 mg/m², or 120 mg/m²) + cisplatin 75 mg/m² on Day 1 of the first 4 cycles, followed by Q3W pembrolizumab 200 mg + tusamitamab ravtansine (150 mg/m², 170 mg/m², or 120 mg/m²) on Day 1 of subsequent cycles
- **Carboplatin combination arm:** participants will receive Q3W pembrolizumab 200 mg + tusamitamab ravtansine (150 mg/m², 170 mg/m², or 120 mg/m²) + carboplatin AUC 5, on Day 1 of the first 4 cycles followed by pembrolizumab 200 mg + tusamitamab ravtansine (150 mg/m², 170 mg/m², or 120 mg/m²) on Day 1 of subsequent cycles

The tolerability of each triplet platinum combination will be assessed in approximately 6 to 18 participants to determine the RDE in each triplet platinum combination arm (carboplatin or cisplatin). It is planned to have a total of 6 participants treated at the RDE in each triplet combination arm (leading to a total of approximately 36 participants treated in Part B). The rules to determine the recommended dose are detailed in Section 6.6.1. The starting DL of tusamitamab ravtansine is 150 mg/m².

If the quadruplet combination investigated in Part C has an acceptable toxicity profile, and as the triplet combination was explored in Part B only in case the quadruplet would not be well tolerated, enrollment in Part B will be stopped as soon as the safety run-in Part C ends.

**PART C:**

The tolerability and safety of the pembrolizumab, tusamitamab ravtansine, platinum-based chemotherapy and pemetrexed combinations will be assessed. Participants can be assigned to either cisplatin or carboplatin, per Investigator choice.

- **Cisplatin combination arm:** participants will receive Q3W pembrolizumab 200 mg + tusamitamab ravtansine (150 mg/m², 170 mg/m², or 120 mg/m²) + pemetrexed 500 mg/m$^2$ (with vitamin supplementation) + cisplatin 75 mg/m² all on Day 1 for the first 4 cycles, followed by Q3W pembrolizumab 200 mg + tusamitamab ravtansine (150 mg/m², 170 mg/m², or 120 mg/m²) + pemetrexed 500 mg/m$^2$ (with vitamin supplementation) on Day 1 of subsequent cycles
- **Carboplatin combination arm:** participants will receive Q3W pembrolizumab 200 mg + tusamitamab ravtansine (150 mg/m², 170 mg/m², or 120 mg/m²) + pemetrexed 500 mg/m$^2$ (with vitamin supplementation) + carboplatin AUC 5 all on Day 1 for the first 4 cycles, followed by Q3W pembrolizumab 200 mg + tusamitamab ravtansine (150 mg/m², 170 mg/m² or 120 mg/m² Q3W) + pemetrexed 500 mg/m$^2$ (with vitamin supplementation) on Day 1 of subsequent cycles

The tolerability of each quadruplet platinum combination (ie, tusamitamab ravtansine, pembrolizumab, pemetrexed, and either cisplatin or carboplatin) will be assessed in approximately 6 to 18 participants to determine the RDE. The rules to determine the recommended dose are detailed in Section 6.6.1. The starting DL of tusamitamab ravtansine is 150 mg/m².

### 4.1.2 Expansion cohorts (Parts A & C)

The Expansion Phase will determine the recommended tusamitamab ravtansine DL for Phase 3 studies based on safety, efficacy, safety, and PK–PD modeling at least 2 DLs of tusamitamab ravtansine, as detailed below.

- In Part A, at least 20 participants will be treated at the RDE (150 mg/m$^2$ Q3W), and at least to 20 participants will be treated at a lower DL (100 mg/m$^2$ Q3W). An optional 10 participants may be treated at an additional DL after these cohorts are completed.
  - If fewer than 3 of 10 participants at 100 mg/m$^2$ have a confirmed objective response, early stopping rules will be applied such that enrollment to this DL will be stopped, and at least 20 participants will then be treated an intermediate DL (120 mg/m$^2$). If the 100 mg/m$^2$ DL is not stopped early, enrollment will continue at this DL to treat at least 20 participants.
- In Part C, at least 20 participants will be treated at the RDE (150 mg/m$^2$ Q3W) and at least 20 participants will be treated at a lower DL (100 mg/m$^2$). An optional 10 participants may be treated at an intermediate DL after these cohorts are completed.
  - If fewer than 4 of 10 participants at 100 mg/m$^2$ have a confirmed objective response, early stopping rules will be applied such that enrollment to this DL will be stopped, and at least 20 participants will then be treated an intermediate DL (120 mg/m$^2$). If the 100 mg/m$^2$ DL is not stopped early, enrollment will continue at this DL to treat at least 20 participants.
- Enrollment into Part C and Part A will be based on Investigator's choice.

For each part, expansion cohorts will be opened for enrollment after completion of the safety Run-In for the considered part. Opening of each cohort and enrollment of participants in each cohort will be defined by the Sponsor based on discussions with the SC and approval of the protocol amendment by health authorities and/or IRB/EC (where applicable).

If it is determined that more than 20 participants are necessary to better assess 1 DL of tusamitamab ravtansine in combination with pembrolizumab, the sample size for this DL will not exceed 30 participants.

### 4.1.3 Duration of the study

The duration of the study for a participant (irrespective of the study part) will include:

- **Screening period:** up to 28 days.

  NOTE: To consider approximately 10 days between screening visit and initiation of therapy to ensure availability of IMP at the site.

- **Treatment period:** once successfully screened, enrolled participants may receive study intervention 4 cycles of cisplatin or carboplatin (Part B and C), and pemetrexed (Part C) and tusamitamab ravtansine and pembrolizumab until confirmed disease progression, unacceptable toxicity, new anticancer therapy initiation, death, or the participant's or investigator's decision to stop the treatment. Each cycle of treatment will last for 3 weeks. After discontinuing study intervention, participants will return to the study site approximately 30 days (±5 days) after the last IMP administration or before the participant receives another anticancer therapy, whichever is earlier, for EOT assessments.
- **Safety follow-up visit:** will be performed 90 (±7 days) days after the last IMP administration. SAEs/AESIs (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. If ongoing related AE/SAE are resolved or stabilized, no further follow-up visit will be needed.
- A participant who stops treatment before documented progressive disease (PD) should undergo tumor assessments every 6 weeks during the first 24 weeks, and then every 9 weeks (±7 days) until radiological disease progression, death, the data cut-off date for secondary endpoints, initiation of further anticancer therapy, or withdrawal of the participant's consent, whichever comes first.

## 4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

### 4.2.1 Participant input into design

Lung cancer is the leading cause of death and only 18% of all lung cancer patients survive 5 years or more after initial diagnosis. 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: Nonsquamous carcinoma (including adenocarcinoma, large-cell carcinoma and other subtypes) and squamous cell (epidermoid) carcinoma. Adenocarcinoma is the most common subtype of NSQ NSCLC (14).

The past decade has dramatically changed the approach on diagnosis and treatment of lung cancer with the concept of personalized medicine, which led to the discovery of several therapeutic options that are only approved for treatment of patients with specific histopathologic characteristics (15).

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

In the 92 NSQ NSCLC patients treated in Study TED13751, tusamitamab ravtansine showed encouraging antitumor activity in 64 heavily pretreated patients with NSQ NSCLC CEACAM5 ≥50%. This antitumor activity was associated with an overall response rate of 20.3% per RECIST◦1.1 (95%◦CI: 12.27%-31.71%), warranting further development of tusamitamab

ravtansine to treat this patient population. In 28 heavily pretreated patients with NSQ NSCLC CEACAM5 ≥1% and <50%, the overall response rate was 7.1% per RECIST◦1.1 (95%◦CI: 1.98%-22.65%). Pembrolizumab is the first approved and the mostly used ICI in the first-line NSCLC in combination with standard of care and as a single agent therapy (6, 16). The combination with an ICI should lead to improve outcomes, as compared to a combination with untargeted, toxic systemic chemotherapy.

### 4.3 JUSTIFICATION FOR DOSE

In the FIH study of tusamitamab ravtansine (TED13751), dose escalation design explored doses between 5 and 150 mg/m$^2$ administered once every 2 weeks (Q2W). The recommended dose was determined as 100 mg/m$^2$ Q2W. In this trial, tusamitamab ravtansine Q3W was evaluated in a dose-escalation cohort of CEACAM5-positive, heavily pretreated patients. No DLT has been observed in participants treated with 120 mg/m², 150 mg/m², or 170 mg/m² tusamitamab ravtansine Q3W. Two DLTs have been reported at the dose of 190 mg/m²: 1 patient experienced Grade 2 keratopathy leading to a dose delay of more than 14 days, and 1 patient experienced Grade 3 AST/ALT increase considered by the investigator to be treatment-related. Based on these findings, 190 mg/m$^2$ is confirmed as the MAD (Maximum Administered Dose). The recommended dose for tusamitamab ravtansine as monotherapy on a Q3W schedule was determined as 170 mg/m² in Study TED13751. In Study ACT16146, the starting tusamitamab ravtansine dose in combination with pembrolizumab and platinum-based chemotherapy, with or without pemetrexed, will be 150 mg/m² Q3W, as it corresponds to the same dose intensity as with the recommended 100 mg/m² Q2W dose (50 mg/m²/week) and well tolerated in the monotherapy Q3W expansion cohort of the FIH. If no DLT is observed among the 3 first participants with good safety profile, after discussion with the Study Committee, the dose may be increased to 170 mg/m² Q3W. The rules will be applicable as described in Section 6.6.1.

After completion of the Safety Run-In part, 2 to 3 DLs including the RDE (150 mg/m$^2$), a lower DL (100 mg/m$^2$), and if needed, an intermediate DL (120 mg/m$^2$), will be evaluated in the expansion phase for Parts A and C to further evaluate the efficacy, safety, and PK of tusamitamab ravtansine to determine the recommended dose for Phase 3 studies. An optional 10 patients may be treated at this additional dose of tusamitamab ravtansine.

This choice is based on safety and PK considerations. Analyses from the FIH study, which evaluated the tusamitamab ravtansine Q2W regimen, demonstrated a significant association between corneal events and tusamitamab ravtansine exposure. The exposure at 100 mg/m$^2$ Q3W is expected to be lower than that with 150 mg/m$^2$ Q3W, which suggests that the lower dosage to be tested in this study may be associated with a decrease in corneal events and a better global safety profile, including fewer SAEs and permanent treatment discontinuations.

In addition to a potential benefit to the safety profile, a lower dosage of tusamitamab ravtansine is hypothesized to be sufficient to achieve clinical efficacy when used in combination with pembrolizumab-based regimens. Nonclinical studies have demonstrated that ADCs synergize with ICIs through induction of immunogenic cell death and recruitment of tumor-infiltrating CD8+ T-cells, thereby expanding the therapeutic benefit of ICIs (1). Maximal tumor cell killing with ADCs may not be required to prime the response to checkpoint blockade, which often depends on

neoantigen release that is not necessarily proportional to cells killed. Specifically, nonclinical studies with combinations of tusamitamab ravtansine and an antibody to murine PD-1 (anti-muPD-1), anti-PD-L1, or anti-murine CTLA-4 surrogate blockade antibody, in a subcutaneous colon MC38 syngeneic tumor implanted in female C57Bl/6 mice, revealed that tusamitamab ravtansine synergized with anti-muPD-1 or an anti-PD-L1 surrogate blockade antibody. When used as single agents, either tusamitamab ravtansine or surrogate blockade antibodies showed marginal activity; however the combination led to robust tumor regression. As such, tusamitimab ravtansine has the ability to both induce direct cytotoxic effects on CEACAM5-expressing tumor cells and stimulate the immune response to certain antigens released by dying cancer cells leading to immunogenic cell death. Therefore, when used in combination with immuno-oncology therapy, a lower dosage of tusamitamab ravtansine may be justified.

Ultimately, the recommened DL for tusamitamab ravtansine in combination with a pembrolizumab-based regimen to be evaluated in Phase 3 studies will be defined based on evaluation of safety and efficacy and PK-PD analyses of at least 2 tested DLs in the Expansion Phase. If at any time the activity observed with tusamitamab ravtansine treatment at the RDE or a lower DL is below expected activity, further enrollment may be considered.

## 4.4 END OF STUDY DEFINITION

The end of the study is defined as the date of the last visit of the last participant or last scheduled procedure shown in the SoA for the last participant in the study. It will occur at the final study cut-off date (estimated at 4.5 months after the last participant's first IMP administration) or when all participants complete the EOT and the Follow-Up visit approximately 90 days after the last IMP administration, whichever is the latest.

# 5 STUDY POPULATION

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

## 5.1 INCLUSION CRITERIA

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

**Age**

I 01. 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-confirmed diagnosis of advanced or metastatic NSQ NSCLC with no EGFR sensitizing mutation or BRAF mutation or ALK/ROS alterations.

I 03. No prior systemic chemotherapy for the treatment of the participant's advanced or metastatic disease (treatment with chemotherapy and/or radiation as part of neoadjuvant/adjuvant therapy is allowed as long as completed at least 6 months prior to diagnosis of advanced or metastatic disease).

I 04. Expression of CEACAM5 as demonstrated prospectively by a centrally assessed IHC assay of ≥2+ in intensity involving at least 1% of the tumor cell population in archival tumor sample (or if not available fresh biopsy sample will be collected if considered an acceptable risk by the treating physician). 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 05. This inclusion criterion was removed in Amended Protocol 03.

I 06. Measurable disease based on RECIST 1.1.

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

**Sex**

I 08. All (male and female)

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

a) Male participants

Male participants are eligible to participate if they agree to the following during the intervention period and for at least 4 months after the last dose of tusamitamab ravtansine or pembrolizumab, and at least 6 months after the last dose of platinum-based chemotherapy or pemetrexed:

- Refrain from donating sperm

PLUS either:

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

OR

- Must agree to use contraception/barrier as detailed below
  - Agree to use a male condom

b) Female participants

A female participant is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies:

- Not a woman of childbearing potential (WOCBP).

OR

- Is a WOCBP and agrees to use a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, as described in Section 10.4 during the intervention period and for at least 7 months after the last dose of study intervention and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period.
- A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) before the first dose of study intervention.
- Additional requirements for pregnancy testing during and after study intervention are located in Section 10.2.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

**Informed Consent**

I 09. Capable of giving signed informed consent, as described in Section 10.1.2, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

**New criterion introduced with amended protocol06**

I 10. Life expectancy of at least 3 months.

## 5.2 EXCLUSION CRITERIA

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

**Medical conditions**

E 01. This exclusion criterion was removed in Amended Protocol 06.

E 02. Medical conditions requiring concomitant administration of strong CYP3A inhibitor (see Section 10.8), unless it can be discontinued at least 2 weeks before the first administration of study intervention and for the entire study treatment period.

E 03. Uncontrolled brain metastases and history of leptomeningeal disease. Patients with previously treated brain metastases may participate provided that:

- they are stable (ie, without evidence of progression by imaging for at least 4 weeks prior to the first administration of study 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.
- Patients with known untreated, asymptomatic brain metastases (ie, no neurological symptoms, no requirements for corticosteroids, no or minimal surrounding edema, and no lesion >1.5 cm) may participate.

E 04. 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 05. History within the last 3 years of an invasive malignancy other than the one treated in this study, with the exception of resected/ablated basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix, or other local tumors considered cured by local treatment.

E 06. History of known acquired immunodeficiency syndrome (AIDS) related illnesses or known HIV disease requiring antiretroviral treatment, or active hepatitis A, B (defined as either positive HbsAg or positive hepatitis B viral DNA test above the lower limit of detection of the assay), or C (defined as a known positive hepatitis C antibody result and known quantitative HCV RNA results greater than the lower limits of detection of the assay) infection. HIV serology will be tested at screening only for participants enrolled at German sites or in any country where mandatory per local requirements.

E 07. History of active autoimmune disease that has required systemic treatment in the past 2 years.

E 08. History of allogeneic tissue/solid organ transplantation.

E 09. Active infection requiring IV systemic therapy within 2 weeks prior to first study intervention administration or active tuberculosis.

E 10. Interstitial lung disease or history of pneumonitis that has required oral or IV steroids.

E 11. 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 12. 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 13. Symptomatic herpes zoster within 3 months prior to screening.

E 14. Significant allergies to humanized monoclonal antibodies.

E 15. Clinically significant multiple or severe drug allergies, intolerance to topical corticosteroids, or severe post-treatment hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear immunoglobulin A [IgA] dermatosis, toxic epidermal necrolysis, and exfoliative dermatitis).

**Prior/concomitant therapy**

E 16. Concurrent treatment with any other anticancer therapy.

E 17. Have received prior chemotherapy treatment for advanced/metastatic NSCLC.

E 18. The patient is a candidate for a curative treatment with either surgical resection and/or chemoradiation.

E 19. 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 any investigational treatment.

E 20. Any prior therapy targeting CEACAM5.

E 21. Any prior treatment with any other anti-PD-1, or PD-L1 or programmed death-ligand 2 (PD-L2), anti-CD137, or anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).

E 22. Any prior maytansinoid treatment (DM1 or DM4 ADC).

E 23. Is receiving systemic steroid therapy ≤3 days prior to the first dose of study therapy or receiving any other form of immunosuppressive medication. Daily steroid replacement therapy or any corticosteroid premedication if applicable are allowed.

E 24. Any radiation therapy to lung >30 Gy within 6 months of first study intervention administration.

E 25. Has received or will receive a live vaccine within 30 days prior to the first study intervention administration.

E 26. Any major surgery within the preceding 3 weeks of the first study intervention administration.

**Prior/concurrent clinical study experience**

E 27. Current participation in any other clinical study involving an investigational study treatment or any other type of medical research.

**Diagnostic assessments**

E 28. Poor organ function as defined by any one of the following:

1. Serum creatinine >1.5 × upper limit of normal (ULN) or 1.0-1.5 × ULN with estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m² as estimated using a modification of diet in renal disease (MDRD) formula.
2. Total bilirubin >1.0 × ULN.
3. AST, ALT >2.5 × ULN or AST, ALT >1.5 × ULN concomitant with ALP >2.5 × ULN. ALP >5 × ULN with normal ALT/AST, for patients with bone metastases.
4. Neutrophils <1.5 × $10^9$/L or platelet count <100 × $10^9$/L or hemoglobulin <9 g/dL (no blood infusion within 2 weeks before screening)
5. 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
6. INR >1.5 unless participant is receiving anticoagulant therapy or within therapeutic range if receiving anticoagulation that would affect the INR

**Other exclusions**

E 29. Individuals accommodated in an institution because of regulatory or legal order; prisoners or participants who are legally institutionalized.

E 30. Any country-related specific regulation that would prevent the participant from entering the study – see Section 10.7 (country-specific requirements).

E 31. 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 32. Participants are employees of the clinical study site or other individuals directly involved in the conduct of the study, or immediate family members of such individuals (in conjunction with Section 1.61 of the ICH-GCP Ordinance E6).

E 33. Any specific situation during study implementation/course that may rise ethics considerations.

E 34. 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.

## 5.3 LIFESTYLE CONSIDERATIONS

No restrictions are required.

## 5.4 SCREEN FAILURES

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

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

## 5.5 CRITERIA FOR TEMPORARILY DELAYING ENROLLMENT

During a regional or national emergency declared by a governmental agency, the Investigator/site should assess the site's capacity to conduct procedures for a new participant to be enrolled into the study before initiating any screening procedures. Site capacity also should be ensured before enrollment of a participant. If the site is unable to adequately follow protocol-mandated procedures, contingency measures proposed in Appendix 11 (Section 10.11).

# 6 STUDY INTERVENTION

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

## 6.1 STUDY INTERVENTIONS ADMINISTERED

**Table 2 - Overview of study interventions administered**

| **Intervention name** | Tusamitamab ravtansine | Pembrolizumab | Cisplatin | Carboplatin | Pemetrexed |
|---|---|---|---|---|---|
| **Type** | Biologic | Biologic | Drug | Drug | Drug |
| **Dose formulation** | Concentrate for solution for infusion | Concentrate for solution for infusion | Lyophilized powder for reconstitution in solution for infusion[a] | Concentrate for solution for infusion[a] | Concentrate for solution for infusion[a] |
| **Unit dose strength(s)** | 5 mg/mL | 25 mg/mL | Lyophilized powder to be reconstituted to 1 mg/mL | 10 mg/mL | 25 mg/mL |
| **Dosage level(s)** | 150 mg/m² (or 170 mg/m² or 120 mg/m²) on Day 1 and then Q3W<br>100 mg/m² (or alternative) on Day 1 and then Q3W<br>BSA will be determined using the most recent weight (assuming it was assessed in a reasonable time frame according to the investigator) and baseline height; dose may not be adjusted if body weight change is ≤5%. For participants with a BSA >2.2 m², the dose will be calculated based on a BSA of 2.2 m². | 200 mg on Day 1 and then Q3W | 75 mg/m² on Day 1 and then Q3W for the first 4 cycles<br>Body surface area (BSA) will be determined using the most recent weight (assuming it was assessed in a reasonable time frame according to the investigator) and baseline height; dose may not be adjusted if body weight change is ≤5%. | AUC 5 mg/mL/min on Day 1 and then Q3W for the first 4 cycles. Carboplatin dose should not exceed 750 mg. The dose should be calculated using the calvert formula and CrCl should be calculated by Cockcroft-Gault equation[b]. | 500 mg/m² on Day 1 and then Q3W. |

| | | | | | |
|---|---|---|---|---|---|
| **Route of administration** | IV infusion[c] over 1 hour 30 minutes after administration of pembrolizumab. | IV infusion[c] over 30 minutes through an IV line containing a sterile, nonpyrogenic, low-protein binding 0.2 micron to 5 micron in-line or add-on filter. | IV infusion[c] over 30 minutes immediately after administration of tusamitamab ravtansine or pemetrexed (where applicable) | IV infusion[c] over 15 to 60 minutes immediately after administration of tusamitamab ravtansine or pemetrexed (where applicable) | IV infusion[c] over 10 minutes after administration of tusamitamab ravtansine |
| **Use** | experimental | active combination component | active combination component | active combination component | active combination component |
| **IMP and NIMP** | IMP | IMP | IMP | IMP | IMP |
| **Packaging and labeling** | Supplied in 30 mL glass vials with a white plastic flip-off cap, containing 125 mg/25 mL tusamitamab ravtansine, labelled with a multilingual booklet. 1 vial per treatment box. | Supplied in single-dose vials containing 100 mg/4 mL pembrolizumab labelled with a multilingual booklet. 1 vial per treatment box. | To be locally sourced as locally available/59arketman where possible. Central sourcing only for the countries where local sourcing is not possible. | To be locally sourced as locally available/marketed where possible. Central sourcing only for the countries where local sourcing is not possible. | To be locally sourced as locally available/marketed where possible. Central sourcing only for the countries where local sourcing is not possible. |
| **[Current/Former name(s) or alias(es)]** | N/A | Keytruda | Refer to labeling for formulation of cisplatin for injection. | Refer to labeling for formulation of carboplatin for injection. | Refer to labeling for formulation of pemetrexed for injection. |

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

*b* Cockcroft-Gault: Total Dose (mg) = (target AUC) × (CrCl + 25); CrCl = (140 – age) × (weight in kg)/serum creatinine (mg/dl) × 72 × (0.85 if female). The CrCl used in the Calvert formula should not exceed 125 mL/min; Maximum carboplatin dose (mg) = target AUC 5 (mg*min/mL) × (125 + 25) = 5 × 150 mL/min = 750 mg

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

After first study administration 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.

After the study cut-off date for ORR (see Section 9.4.1), patients with observed clinical benefit who are still receiving study treatment can continue study treatment.

Study intervention will be administered until confirmed disease progression, unacceptable toxicity, new anticancer therapy initiation, death, or the participant's or investigator's decision to stop the treatment.

***Noninvestigational medicinal product:***

***Premedication for tusamitamab ravtansine***

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

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

Premedication will be supplied by the study sites. If oral diphenhydramine is not available, other Histamine H1 antagonist or other form of diphenhydramine can be given per local label and clinical practice.

**Vitamin supplementation for pemetrexed**

All subjects should receive the appropriate supplementation of vitamin B12 and folic acid and corticosteroid prophylaxis as listed below (or as per local label):

- Folic Acid 350-1000 µg oral: at least 5 doses of folic acid must be taken during the 7 days preceding the first dose of pemetrexed, and folic acid dosing must continue during the full course of therapy and for 21 days after the last dose of pemetrexed.
- Vitamin B12 1000 µg IM injection in the week preceding the first dose of pemetrexed and once every 3 cycles thereafter. Subsequent vitamin B12 injections may be given the same day as pemetrexed administration.
- Dexamethasone prophylaxis 4 mg, orally twice per day (or equivalent). Taken the day before, day of, and day after pemetrexed administration. Higher or additional doses are permitted for antiemetic prophylaxis during Cycles 1-4 but not to exceed doses in MASCC guidelines (Section 10.10).

## 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.

Any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) must be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure (see Section 8.3.9).

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

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

Treatment preparation and administration (including compatible materials) will be further detailed in the pharmacy manual.

## 6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Not applicable.

## 6.4 STUDY INTERVENTION COMPLIANCE

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

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

## 6.5 CONCOMITANT THERAPY

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

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

Concomitant medications 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 Aes.

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

- Palliative radiotherapy may be given for control of pain (for palliative 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.
- 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 participant's wellbeing may be prescribed at the Investigator's discretion. Every medication or treatment taken by the participants during the trial and the reason for its administration must be recorded on the eCRF.

The following treatments are not permitted during this study:

- Other investigational drugs.
- Any other anticancer therapy not specified in the protocol, including immunotherapy, hormonal therapy, targeted therapy, or biological therapies.
- Primary prophylactic use of Granulocyte-Colony Stimulating Factor is not allowed during the DLT observation period. Secondary prophylaxis or therapeutic administration is allowed.
- Prophylactic erythropoietin during the first cycle.
- Concomitant use of strong CYP3A inhibitors (see Section 10.8) should be avoided from 2 weeks before tusamitamab ravtansine administration up to the last tusamitamab ravtansine administration.
- The use of contact lenses will not be permitted during the study treatment period.

## 6.6 DOSE MODIFICATION

### 6.6.1 Determination of recommended doses

During Part A, the RDE of tusamitamab ravtansine in combination with pembrolizumab will be determined for the expansion cohort according to the DLTs observed in participants receiving the combination study intervention and other available relevant information, including the overall safety and efficacy.

During Part B, the RDE of tusamitamab ravtansine in combination with pembrolizumab and platinum-based chemotherapy will be determined according to the DLTs observed in participants receiving the combination with cisplatin or with carboplatin and other available relevant information, including the overall safety and efficacy.

During Part C, the RDE of tusamitamab ravtansine in combination with pembrolizumab, platinum-based chemotherapy and pemetrexed will be determined according to the DLTs observed in participants receiving the combination with cisplatin or with carboplatin and other available relevant information, including the overall safety and efficacy.

Definitions of DLTs are provided in Table 3.

**Table 3 - Definition of dose-limiting toxicity**

| Type of abnormality | Details |
|---|---|
| Hematological abnormalities | Grade 4 neutropenia for 7 or more consecutive days |
| | Grade 3 to 4 neutropenia complicated by fever (temperature ≥38.5°C on more than 1 occasion) or microbiologically or radiographically documented infection |
| | Grade ≥3 thrombocytopenia associated with clinically significant bleeding requiring clinical intervention |
| Nonhematological abnormalities | Grade 4 non-hematologic AE, except AE symptoms related to the underlying disease as per the investigator's judgment |
| | Grade ≥3 keratopathy |
| Miscellaneous | 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 |

The DLT observation period is the first cycle (21 days; duration will be longer for participants who delay initiation of Cycle 2 due to treatment-related AE whose duration must be assessed to determine whether this AE meets the definition of a DLT). Depending on the DLTs observed, DLs of tusamitamab ravtansine can be tested during the safety run-in phase of the study in Part A, Part B, and Part C: 150 mg/m², 170 mg/m², and 120 mg/m².

For each DL of the combination arms (starting dose, DL plus 1 [DL+1] and DL minus 1 [DL-1], if applicable), a minimum of 1 week is mandatory between the first dose of the first participant treated at this DL and the first dose of the next participant treated at the same DL. Once 3 participants have been treated at this DL and are DLT-evaluable, the tolerability of the combination is assessed according to the following algorithm, as depicted in Figure 1.

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

Dose modification and dose schedules are shown in Table 4. The decision tree for tusamitamab ravtansine doses is summarized in Figure 1. The Study Committee will review clinical data, on a regular basis, approximately every 2 weeks during the study (Section 10.1.4) and will decide on whether to escalate to the next DL, de-escalate, stay at the current DL, or to add alternative DLs. Dosage decisions for the doublet combination, triplet combinations, and quadruplet combinations will be discussed during this Study Committee meeting and will be clearly documented in the meeting minutes. Beyond recommended dose selection driven by DLT incidence, the SC could decide to explore lower DLs to better support final dose selection. Ultimately, the overall safety and efficacy will be evaluated in totality to determine the RDE.

**Table 4 - Dose levels (safety run-in part)**

| Dose level (DL) | Tusamitamab ravtansine | Pembrolizumab | Cisplatin (Cycles 1-4) | Carboplatin (Cycles 1-4) | Pemetrexed |
|---|---|---|---|---|---|
| Starting dose | 150 mg/m² Q3W | 200 mg Q3W | 75 mg/m² Q3W | AUC 5 mg/mL/min Q3W | 500 mg/m² Q3W |
| Plus 1 (DL+1) | 170 mg/m² Q3W | 200 mg Q3W | 75 mg/m² Q3W | AUC 5 mg/mL/min Q3W | 500 mg/m² Q3W |
| Minus 1 (DL-1) | 120 mg/m² Q3W | 200 mg Q3W | 75 mg/m² Q3W | AUC 5 mg/mL/min Q3W | 500 mg/m² Q3W |

DL=dose level; Q3W=every 3 weeks.
For participants with a BSA >2.2 m², the dose of tusamitamab ravtansine will be calculated based on a BSA of 2.2 m².
Note: In case a participant is treated at a tusamitamab ravtansine DL, and the Study Committee decides another DL to be the recommended dose, the participant will continue to be treated at the participant's initial DL unless individual dose modification is required (Section 6.6).

### 6.6.2 Individual dose modification

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

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

The dose may be adjusted if body weight change is >5%. Dose adjustment and/or cycle delays are permitted in case of adverse reaction. In case of toxicity, cycle delays and dose modifications should be implemented to manage adverse reactions according to Section 10.6 (Table 10 for tusamitamab ravtansine, Table 11 for pembrolizumab, Table 12 for cisplatin/carboplatin and pemetrexed hematologic toxicity and Table 13 for cisplatin/carboplatin and pemetrexed nonhematologic toxicity). Every effort will be made to administer the full dose regimen and maximize dose intensity. Recommended dose modifications for key chemotherapy toxicities serve as a guide and do not replace investigator judgment and applicable local label recommendations if more stringent.

Dose modification 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 modification recommended should be followed.

The acceptable treatment window is 3 days. Dose delay is allowed for safety management. Retreatment of patients that require more than 6 weeks' dose delay need to be justified with case-by-case risk-benefit assessment. See Section 10.6 (Table 10, Table 11, Table 12, and Table 13) for guidance in dose modification or discontinuation.

Administration of the study treatment will be discontinued in the event of a TEAE that persists despite appropriate cycle delay or any other AE that, in the opinion of the Investigator, warrants discontinuation. All changes to study treatment administration must be recorded in the eCRF.

Recommendations in the event of neutropenia are provided in Section 8.3.11.4.

Pembrolizumab dose reduction is not recommended. Approved product labels should be followed for patients receiving pembrolizumab, cisplatin/carboplatin or pemetrexed treatment for supportive care and dose modification requirement due to not listed Aes. Reduction of tusamitamab ravtansine, cisplatin/carboplatin, or pemetrexed and not pembrolizumab is appropriate if, in the opinion of the Investigator, the toxicity is clearly related to the other agent not pembrolizumab.

If appropriate, and if in the opinion of the Investigator, the toxicity is related to one of the treatments, pembrolizumab, tusamitamab ravtansine, cisplatin/carboplatin or pemetrexed instead of the combination and more than 1 cycle delay is needed, this drug may be interrupted upon discussion with the Sponsor, and the other drug(s) can be continued and this drug can only be resumed at following cycle after the toxicity recovers to Grade ≤1. If the toxicity is related to the combination of several agents (pembrolizumab, tusamitamab ravtansine, cisplatin/carboplatin or pemetrexed), all agents should be reduced (if applicable), interrupted or permanently discontinued according to the recommended dose modifications. If one of the drugs (pembrolizumab, tusamitamab ravtansine, cisplatin/carboplatin or pemetrexed) is prematurely permanently discontinued, the other drug(s) can be continued until the conditions for treatment discontinuation as described in Section 6.1 are met.

One dose reduction is allowed for tusamitamab ravtansine due to safety reason. Once the dose is reduced, it is permanently reduced. During the conduct of the study, second dose reduction of tusamitamab ravtansine may be needed, and need to be decided case by case discussion with the Sponsor. In case a dose reduction is necessary, dose reduction of tusamitamab ravtansine will be administered as follows:

**Table 5 - Individual tusamitamab ravtansine dose reduction**

| Drug name | Initial dose | 1st reduced dose | 2nd reduced dose |
|---|---|---|---|
| Tusamitamab ravtansine | 170 mg/m$^2$ Q3W | 150 mg/m$^2$ Q3W | 120 mg/m$^2$ Q3W |
| Tusamitamab ravtansine | 150 mg/m$^2$ Q3W | 120 mg/m$^2$ Q3W | 100 mg/m$^2$ Q3W |
| Tusamitamab ravtansine | 120 mg/m$^2$ Q3W | 100 mg/m$^2$ Q3W | 80 mg/m$^2$ Q3W |
| Tusamitamab ravtansine | 100 mg/m$^2$ Q3W | 80 mg/m$^2$ Q3W | - |

A participant can have a maximum of 2 dose modifications (if applicable) to cisplatin/carboplatin or pemetrexed dosing for toxicities throughout the course of the study. A participant who requires a third dose modification to any particular component will have that agent discontinued.

**Table 6 - Individual cisplatin/carboplatin and pemetrexed dose reduction**

| Drug name | Initial dose | Dose reduction level -1 | Dose reduction level -2 |
|---|---|---|---|
| Cisplatin | 75 mg/m$^2$ | 56 mg/m$^2$ | 38 mg/m$^2$ |
| Carboplatin | AUC 5<br>Maximum dose<br>750mg | AUC 3.75<br>Maximum dose<br>562.5mg | AUC 2.5<br>Maximum dose<br>375mg |
| Pemetrexed | 500 mg/m$^2$ | 375 mg/m$^2$ | 250 mg/m$^2$ |

## 6.7 INTERVENTION AFTER THE END OF THE STUDY

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

## 6.8 TREATMENT OF OVERDOSE

An overdose if a treatment is given via infusion as an increase of at least 30% of the dose to be administered in the specified duration or if the dose is administered in less than half the recommended duration of administration.

The Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the Investigator should:

- Contact the Medical Monitor immediately.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities.
- Obtain a plasma sample for PK analysis if requested by the Medical Monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

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

# 7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

## 7.1 DISCONTINUATION OF STUDY INTERVENTION

### 7.1.1 Permanent discontinuation

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

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

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

If a participant in a combination arm prematurely permanently discontinues only one of the IMPs, the other IMP(s) can be continued until the conditions for treatment discontinuation as described in Section 6.1 are met.

See Section 10.6 (Table 10, Table 11, Table 12, and Table 13) for more details on discontinuation.

See the SoA (Section 1.3) for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed. Any abnormal laboratory value or ECG parameter will be immediately rechecked for confirmation (please specify, eg, after 24 hours) before making a decision of permanent discontinuation of the IMP for the concerned participant.

**Handling of participants after permanent 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 permanent discontinuation of intervention, the participants will be assessed using the procedure normally planned for the last dosing day with the IMP tumor assessment, safety laboratory assessment and immunogenicity sample, if appropriate.

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

### 7.1.2 Temporary discontinuation

Temporary intervention discontinuation may be considered by the Investigator because of suspected Aes. For all temporary intervention discontinuations, duration should be recorded by the Investigator in the appropriate pages of the eCRF.

See Section 10.6 (Table 10, Table 11, Table 12 and Table 13) for more details on discontinuation.

If the temporary discontinuation corresponds to more than 6 weeks delay of study intervention, all measures should be taken to ensure the participant's wellbeing, and the management plan for each ongoing patient should be guided by the clinical judgment of the treating physician based on an individual benefit-risk assessment and the evolving emergency situation.

#### *7.1.2.1 Rechallenge*

Reinitiation of intervention with the IMP will be done under close and appropriate clinical/and or laboratory monitoring once the Investigator will have considered according to his/her best medical judgment that the responsibility of the IMP(s) in the occurrence of the concerned event was unlikely and if the selection criteria for the study are still met (refer to Section 5).

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 11 (Section 10.11). During a regional or national emergency declared by a governmental agency, reinitiation of IMP after temporary discontinuation can occur only once the Investigator has determined, according to his/her best judgment, that the participant would likely benefit from continued study treatment, and the IMP(s) was unlikely to contribute to the occurrence of an event of epidemic (eg, COVID-19). The Investigator should discuss the restart of IMP after prolonged cycle delay with Sponsor's Medical Monitor.

## 7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

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

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

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

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

In addition, a participant may withdraw his/her consent to 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.

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 Section 10.1.

# 8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- In the event of a significant study-continuity issue (eg, caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution and monitoring may be implemented by the Sponsor or the Investigator, as per local Health Authority/ethics requirements (see Appendix 11 [Section 10.11]).
- Tumor CEACAM5 expression, tumor PD-L1 expression status, circulating CEA and age will be collected during the prescreening visit.
- During screening period, demography, medical/surgical, and disease history will be evaluated. Demography includes, 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, previous antitumor therapy (type, start and end dates, reason for discontinuation and response to the therapy, and date of relapse/progression), previous surgery for NSCLC, and smoking history.
- For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 11 (Section 10.11).

## 8.1 EFFICACY ASSESSMENTS

All efficacy endpoints are based on tumor assessment. Schedule of tumor assessments is provided in SoA. Assessment of antitumor activity of tusamitamab ravtansine based on ORR per RECIST v1.1 is the primary efficacy objective.

Tumor assessment method per RECIST 1.1 is detailed in Section 10.9. 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 first 24 weeks, and then every 9 weeks until radiological disease progression, initiation of further anticancer therapy, death, or the data cut-off for secondary endpoints, whichever comes first. 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.

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

Brain CT-scan or MRI should be performed at baseline only if clinically indicated and followed only for patients with brain lesions at baseline.

Objective response rate (ORR) will be derived based on investigator review at each time point at which a response assessment occurred using the RECIST 1.1 (see Section 10.9).

The secondary endpoints (DOR, PFS, and DCR) will also be derived.

Participants who stopped treatment before documented progressive disease (PD) should undergo a tumor assessment every 6 weeks during the first 24 weeks, and then every 9 weeks (±7 days) until radiological disease progression, death, the data cut-off date for secondary endpoints, initiation of further anticancer therapy, or withdrawal of the participant's consent, whichever comes first. Participants with or without documented disease progression should attend an on-site follow-up visit 90 days after the last dose of study medication.

## 8.2 SAFETY ASSESSMENTS

Planned time points for all safety assessments are provided in the SoA.

### 8.2.1 Physical examinations

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

### 8.2.2 Performance status

- Performance status will be evaluated using ECOG scale (17).

### 8.2.3 Specific ocular test

Standard specific ocular tests by an ophthalmologist include:

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

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

In participants with any ocular/visual symptom(s) (eg, blurred vision, photophobia) the complete ocular tests will be repeated at the time of the occurrence of the ocular toxicity, if any regardless of the grade. Then, visual acuity, slit lamp examination under dilatation, and Schirmer's test will be repeated once weekly (if not recommended to have less frequent 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.

### 8.2.4 Vital signs

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

### 8.2.5 Electrocardiogram

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

### 8.2.6 Clinical safety laboratory assessments

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- Clinical safety assessments will be conducted at each cycle. Tests can be performed on the same day or within the 2 days before initiating study intervention. During first 2 cycles, hematology and liver function tests (ie, ALT, AST, ALP, total and direct bilirubin) will be assessed weekly. Tests can be done 1 day before or after the planned date. If Grade 4 neutropenia occurs, ANC will be assessed every 2 to 3 days until ANC $\geq 0.5 \times 10^9$/L. In case of a Grade ≥3 abnormality in liver function tests, additional tests will be done every 2 to 3 days until recovery to baseline value. Additional tests will be performed when clinically appropriate.
- The Investigator must review the laboratory report and document this review. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.

- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.
  - If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified.
  - All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the SoA.
  - If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

## 8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

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).

### 8.3.1 Time period and frequency for collecting AE and SAE information

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

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

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

### 8.3.2 Method of detecting Aes and SAEs

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

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

### 8.3.3 Follow-up of Aes and SAEs

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

### 8.3.4 Regulatory reporting requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.
- Adverse events that are considered expected will be specified in the reference safety information (IB).
- 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.
- An Investigator who receives an Investigator safety report describing an SAE, SUSAR or any other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements. It is the responsibility of the Sponsor to assess whether an event meets the criteria for a SUSAR, and therefore, is expedited to regulatory authorities.

### 8.3.5 Pregnancy

- Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study intervention and until 7 months after the last dose of study intervention.

- If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 8.3.4.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

### 8.3.6 Cardiovascular and death events

Cardiovascular events will be treated as regular events. Refer to Section 8.3.7 for specificities linked to death events.

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

Not applicable.

### 8.3.8 Adverse event of special interest

**Adverse event of special interest**

An AESI is an AE (serious or 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 participant entered in a study as well as pregnancy occurring in a female partner of a male participant 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 Section 8.3.5).
- Grade ≥3 keratopathy
- Bundle branch blocks or any conduction defects
- Grade ≥3 liver enzyme increased (symptomatic or asymptomatic)
- Symptomatic overdose (serious or 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 (not based on systematic pills count) and defined as an increase of at least 30% of the dose to be administered in the specified duration or if the dose is administered in less than half the recommended duration of administration.
- Dose-limiting toxicity as defined in Section 6.6.1.

### 8.3.9 Overdose, medication errors, misuses or abuses of medicinal product

All reports of overdose, medication error, misuse or abuse in relation to the IMP with or without an AE must be recorded on the corresponding page(s) of the CRF and transmitted to the Sponsor's representative following standard processes. The Investigator will assess whether or not the overdose, medication error, misuse or abuse event has to be reported together with an AE or SAE.

An overdose definition is given in Section 6.8.

A medication error is an unintended failure in the drug treatment process (ie, mistake in the process of prescribing, storing, dispensing, preparing, or administering medicinal products in clinical practice) that leads to, or has the potential to lead to harm to the participant.

A misuse refers to situations where the medicinal product is intentionally and inappropriately used, ie, not in accordance with the terms of the marketing authorization or outside what is foreseen in the protocol, by the participant for a therapeutic purpose.

An abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects, ie, intentional non-therapeutic use of a medicinal product by a participant for a perceived reward or desired non-therapeutic effect including, but not limited to, "getting high"(euphoria).

This includes situations in which a participant was involved or not (eg, even if the error was recognized and intercepted before the participant received or used the product), and whether it resulted in harm to the participant or not. Of note, if a medication error or misuse meets the protocol definition of an overdose, it will be recorded in the overdose page of the CRF.

### 8.3.10 Guidelines for reporting product complaints

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

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

### 8.3.11 Guidelines for managing specific adverse events

#### *8.3.11.1 Hypersensitivity reactions*

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

In case of event of hypersensitivity reactions, please refer to the recommended dose modification or discontinuation table (Table 10 and Table 11) in Appendix 6 (Section 10.6).

#### *8.3.11.2 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 SoA. If ocular symptoms are present before IMP infusion, then a formal ocular examination should be performed. In patients with any ocular/visual symptom(s) (eg, blurred vision, photophobia, etc) the ocular evaluation should be repeated once weekly if not less frequent assessment recommended by ophthalmologist based on lesion characteristics, until resolution to Grade 1. Photographs of the cornea are recommended to be taken at the site, if possible, when ocular findings are first documented and to follow progression when relevant. Tonometry and additional ocular assessment can be performed at discretion of ophthalmologist when applicable.

##### *8.3.11.2.1 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 PT unless otherwise specified by ophthalmologist due to inflammatory findings on eye exams leading to diagnosis of keratitis.

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

No primary prophylaxis is recommended but prevention of dry eye with artificial tears and avoidance of using contact lenses should be ensured during treatment period. Corticosteroid containing ocular drugs are recommended in case ocular symptom occurs for the management of keratopathy/keratitis and treatment will be performed at the discretion of ophthalmologist. Dose modification and recommendations are further described in Section 10.6.

#### *8.3.11.3 Management of anemia*

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

#### *8.3.11.4 Management of neutropenia*

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

If the patient continues to experience these reactions at lower dose, the treatment should be discontinued as describe in Section 6.6.2.

Dose modification and recommendations are further described in Section 10.6.

#### *8.3.11.5 Liver function tests*

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

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

#### *8.3.11.6 Immune-related adverse reactions*

Immune-related adverse reactions have been reported with pembrolizumab administration and the following procedures should be followed:

- Immune-mediated pneumonitis: withhold for Grade 2, and permanently discontinue for Grade 3, Grade 4 or recurrent Grade 2 pneumonitis.
- Immune-mediated colitis: withhold for Grade 2 or 3, and permanently discontinue for Grade 4 or recurrent Grade 3 colitis.
- Immune-mediated hepatitis: monitor for changes in hepatic function. Based on severity of liver enzyme elevations, withhold or discontinue pembrolizumab. Consider corticosteroid therapy.
- Immune-mediated endocrinopathies:
  - Hypophysitis: withhold for Grade 2 and withhold or permanently discontinue for Grade 3 or 4 hypophysitis.
  - Thyroid disorders: monitor for changes in thyroid function. Withhold or permanently discontinue for Grade 3 or 4 hyperthyroidism.
  - Type 1 diabetes mellitus: monitor for hyperglycemia. Withhold pembrolizumab in cases of Grade 3 hyperglycemia.
- Immune-mediated nephritis: monitor for changes in renal function. Withhold for Grade 2, and permanently discontinue for Grade 3 or 4 nephritis.

- Immune-mediated skin adverse reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN): withhold for Grade 3 and permanently discontinue for Grade 4 skin reactions.

#### *8.3.11.7 Peripheral neuropathy*

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

#### *8.3.11.8 Colitis (including hemorrhagic)*

In Study TED13751 evaluating tusamitamab ravtansine in patients with several cancer types, a limited number of participants developed colitis. Based on clinical observations, patients with known underlying colitis or gastrointestinal tract conditions are noted to be at highest risk for such events. Cycle delays or modifications for symptoms of colitis should be compliant with Section 6.6.2.

### 8.4 PHARMACOKINETICS

Blood samples will be collected for the measurement of tusamitamab ravtansine (SAR408701, DM4, Me-DM4), pembrolizumab, cisplatin or carboplatin and pemetrexed concentrations as described in the PK/ATA flowcharts (Section 1.3.2). 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.

Samples collected for analyses of tusamitamab ravtansine concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

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

Concentrations of tusamitamab ravtansine (SAR408701, DM4, Me-DM4), pemetrexed and cisplatin or carboplatin will be used for population PK analysis by nonlinear mixed-effects modeling. Empirical Bayesian estimation of individual exposure parameters such as maximum concentration ($C_{max}$), trough concentration ($C_{trough}$) and area under the curve (AUC) will be derived.

Pembrolizumab $C_{trough}$ values for Part A, Part B and Part C will be reported.

## 8.5 PHARMACODYNAMICS

Circulating CEA levels will be collected at prescreening, baseline and during the treatment period at the time of laboratory assessment as close as possible to tumor assessment (and no more than 2 weeks from the tumor assessment) until EOT. It will be assessed using local testing. For CEA sample collection scheduled on the day of a treatment visit, samples should be drawn prior to initiation of any IMP infusion.

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

## 8.6 GENETICS

### 8.6.1 Plasma cfDNA

A 20 mL blood sample corresponding to about 10 mL of plasma for tumor cfDNA isolation will be collected at pre-infusion of Cycle 1 Day 1 and Cycle 5 Day 1. At Cycle 1 Day 1 an additional 2 mL blood sample for germline DNA.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

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

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

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

### 8.6.2 Tumor DNA and RNA analyses

Although tumor CEACAM5 expression is a major parameter driving the activity of an antiCEACAM5 ADC such as tusamitamab ravtansine, other factors may significantly contribute. Tumor tissue will therefore also be requested if enough tissue is available to explore the potential relationship between clinical endpoints following tusamitamab ravtansine therapy and potential sets of biomarkers besides target expression that could be predictive of response. For that purpose, 3 × 10 µm slides (or equivalent such as 6 × 3-5 µm or other) from the same sample as the one sent for CEACAM5 assessment at prescreening are requested if enough tissue material

is available at screening or Cycle 1 Day 1. An additional section at 5 µm should be sent for hematoxylin-eosine staining. The samples may serve to investigate other potential biomarkers of response. In tumor tissue, biomarker annotation could include, but may not be restricted to, genomic annotation by sequencing, gene copy number variation, gene expression (mRNA and miRNA), and proteomic profiling.

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

## 8.7 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:
  - Blood sample will be collected for IgG dosage to explore impact of IgG level on PK of tusamitamab ravtansine.
  - Tumor tissue samples will be collected and assayed for CEACAM5 expression to determine eligibility for this study.
  - Blood sample will be collected for circulating tumoral cell (CTC) detection to assess the expression of CEACAM5 on these cells (optional).
- Instructions for the collection and handling of biological samples will be provided by the Sponsor in a separate laboratory manual.
- The level of IgG in blood at pre-infusion of Cycle 1 Day 1 will be determined by a central laboratory. For this test 2 mL of blood will be collected, corresponding to 1mL of serum.
- The level of CEACAM5 expression in tumor tissues will be determined by a central laboratory using CEACAM5 IHC 769 assay provided by a third party. CEACAM5 IHC 769 is a qualitative immunohistochemical assay using monoclonal mouse anti-CEACAM5, Clone 769 intended for use in the detection of CEACAM5 protein in FFPE nonsquamous NSCLC tissue using EnVision FLEX visualization system on Dako Omnis platform.
- Assessment of CTC at pre-infusion of Cycle 1 Day 1 will be determined by a central laboratory. For this test, 10 mL of blood will be collected. Sample will be taken in a maximum of 10 participants.

## 8.8 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 1.3.2). These samples will be tested by the Sponsor's designee.

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

A 3-tiered approach will be employed to assess the immunogenicity of tusamitamab ravtansine when applicable: Samples will be screened and then confirmed for antibodies binding to tusamitamab ravtansine and the titer of confirmed positive samples will be reported. Other analyses may be performed to further characterize the immunogenicity of tusamitamab ravtansine.

## 8.9 HEALTH ECONOMICS

No health economics data will be collected.

## 8.10 USE OF BIOLOGICAL SAMPLES AND DATA FOR FUTURE RESEARCH

Future research may help further the understanding of disease and development of new medicines. Reuse of coded data and biological samples (leftover and additional) will be limited to future scientific research conducted under a research plan for the purpose of diagnosing, preventing, or treating diseases. The future research projects will be conducted under the Sponsor's and/or its affiliates' and/or, if applicable, the partner of the Sponsor which has licensed the study drug to the Sponsor or which is co-developing the study drug with the Sponsor's control, acting alone or in collaboration with research partners such as universities, research institutions or industrial partners with whom the coded data may be shared.

Data and biological samples will be stored and used for future research only when consented to by participants (see Section 10.1.2) and, when applicable, further information on the future research has been provided to the study participant, unless prohibited by local laws or IRBs/IECs (in such case, consent for future use of sample will not be included in the local ICF). The conditions for reuse will be adapted locally with the appropriate language in the ICF.

In any case, a specific consent will be collected for the performance of genetic analyses on leftover and/or additional samples.

**Data protection – Processing of coded clinical data**

The study participant will be provided will all mandatory details of the data processing in Section 2 of the core ICF.

The Sponsor adopts safeguards for protecting participant confidentiality and personal data (Section 10.1.3).

**Use of leftover samples and additional samples for future research**

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

The study participant will be provided with all mandatory details of the use of the human biological samples (leftover and additional) in Section 2 of the Core ICF.

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

# 9 STATISTICAL CONSIDERATIONS

## 9.1 STATISTICAL HYPOTHESES

**PART A:**

Safety run-in of Part A aims to establish the RDE of tusamitamab ravtansine in combination with pembrolizumab according to DLTs observed.

Expansion of Part A is designed to obtain preliminary efficacy, safety, and PK data on tusamitamab ravtansine administered in combination with pembrolizumab. As the expansion part is not intended to explicitly test a hypothesis, calculations of power and Type I error were not considered in the study design.

**PART B:**

The Safety run-in of Part B of the study aims to establish the RDEs of tusamitamab ravtansine in combination with pembrolizumab and platinum-based chemotherapy (cisplatin or carboplatin) according to DLTs observed.

**PART C:**

The Safety run-in of Part C of the study aims to establish the RDEs of tusamitamab ravtansine in combination with pembrolizumab, pemetrexed and platinum-based chemotherapy (cisplatin or carboplatin) according to DLTs observed.

The Expansion of Part C is designed to obtain preliminary efficacy, safety, and PK data on tusamitamab ravtansine administered in combination with pembrolizumab, pemetrexed and platinum-based chemotherapy (cisplatin or carboplatin). As the expansion part is not intended to explicitly test a hypothesis, calculations of power and Type I error were not considered in the study design.

For Parts A and C, the expansion part is designed to optimize dose selection to maximize the treatment benefit and to minimize the toxicity (dose optimization).

## 9.2 SAMPLE SIZE DETERMINATION

**PART A:**

The actual sample size is expected to vary depending on DLTs observed. It is anticipated that 6 to 62 participants will be treated with tusamitamab ravtansine + pembrolizumab: up to 12 DLT-evaluable participants at a DL other than the RDE in the safety run-in, at least 20 participants at the RDE (including participants at the RDE from the safety run-in) and a total of 20 to 30 participants at a DL lower than the RDE (100 mg/m$^2$ Q3W) or at an intermediate DL (120 mg/m$^2$). At the 100 mg/m$^2$ DL, early stopping rules will be applied based on an interim analysis (ie, fewer than 3 of 10 participants achieve a confirmed objective response). If the 100 mg/m$^2$ DL is stopped early,

at least 20 participants will then be treated at an intermediate DL (120 mg/m$^2$). If the 100 mg/m$^2$ DL is not stopped early, at least 20 participants will be treated at this DL. An optional 10 participants may be treated at an additional DL which may range from 100 to 150 mg/m$^2$. This DL will be determined by PK modeling, safety, and efficacy of the RDE and lower DL cohorts.

Assuming a prescreening failure rate of 80% (as per the initial protocol) and a study screening failure rate of 20%, approximately 38 to 388 participants would be prescreened to achieve approximately 62 participants. Assuming a prescreening failure rate of 45% the number of participants to be prescreened could significantly be decreased (approximately 141 participants need to be prescreened to achieve 62 participants).

**PART B:**

The actual sample size could vary depending on DLTs observed. It is anticipated that in each triplet combination arm, 6 to 18 participants will be treated with tusamitamab ravtansine + pembrolizumab + cisplatin or carboplatin: including up to 12 DLT-evaluable participants in each triplet combination arm at DL other than the RDE and 6 DLT-evaluable participants in each triplet combination arm at the RDE.

Assuming a prescreening failure rate of 80% (as per the initial protocol) and a study screening failure rate of 20%, approximately 75 to 225 participants will be prescreened to achieve 12 to 36 DLT-evaluable participants in Part B. Assuming a prescreening failure rate of 45%, the number of participants to be prescreened could significantly be decreased (approximately 82 participants need to be prescreened to achieve 36 participants).

**PART C:**

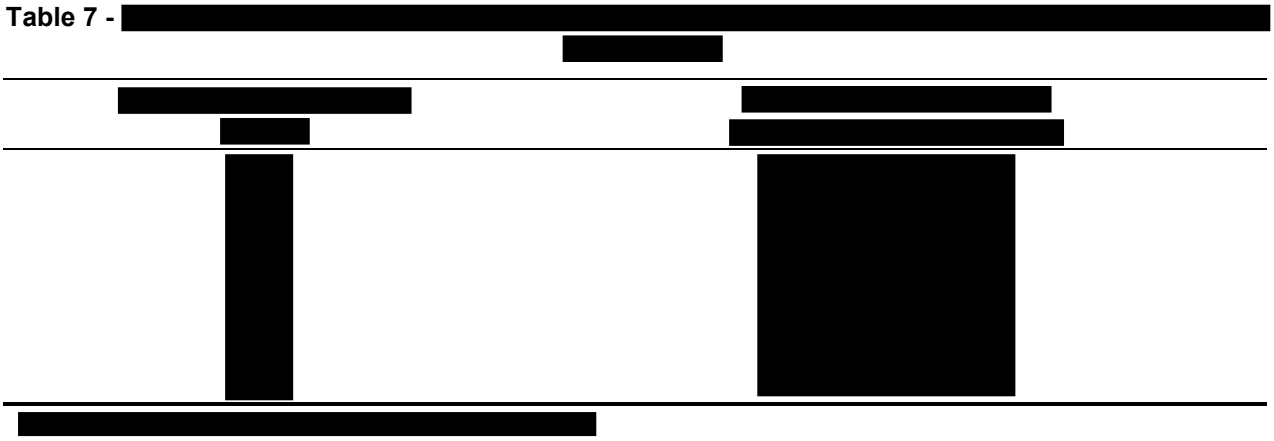
The actual sample size could vary depending on DLTs observed. It is anticipated that, overall, 12 to 74 participants will be treated with tusamitamab ravtansine + pembrolizumab + pemetrexed + cisplatin or carboplatin: up to 12 DLT-evaluable participants in each quadruplet combination arm treated at a DL other than the RDE; at least 20 participants treated at the RDE (regardless of the quadruplet platinum combination, and including participants at the RDE (150 mg/m$^2$) from the safety run-in), and a total of 20 to 30 participants treated at a lower DL (100 mg/m$^2$ Q3W) or at an intermediate DL (120 mg/m$^2$). At the 100 mg/m$^2$ DL, early stopping rules will be applied based on an interim analysis (ie, fewer than 4 of 10 participants achieve a confirmed objective response). If the 100 mg/m$^2$ DL is stopped early, at least 20 participants will then be treated at an intermediate DL (120 mg/m$^2$). If the 100 mg/m$^2$ DL is not stopped early, at least 20 participants will be treated at this DL. An optional 10 participants may be treated at an additional DL which may range from 100 to 150 mg/m$^2$. This dose will be determined by PK modeling, safety, and efficacy of the RDE and lower DL cohorts.

Assuming a prescreening failure rate of 45% and a study screening failure rate of 20%, approximately 28 to 169 participants will be prescreened to achieve 12 to 74 participants in Part C.

Note: “Enrolled” means a participant’s agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

[redacted] Table 7.

**Table 7 - [redacted]**



## 9.3 POPULATIONS FOR ANALYSES

The following populations are defined (Table 8):

**Table 8 - Populations for analyses**

| Population | Description |
|---|---|
| Prescreened | All participants who signed the prescreening informed consent for CEACAM5 assessment of their biopsy. |
| Screened | All participants who signed screening informed consent for study participation. |
| All-treated | All participants assigned to study intervention and who have actually received at least 1 dose of study intervention. |
| DLT-evaluable | Participants who received 1 cycle with at least 80% of the intended dose for each IMP of the combination during the safety run-in part of Part A, Part B or Part C. Participants should have completed Cycle 1 unless they experienced a DLT before the end of Cycle 1. |
| PK | All treated participants with at least 1 available concentration result postbaseline (whichever the cycle and even if dosing is incomplete) with adequate documentation of date and time of dosing and date and time of sampling. |
| ATA | All treated participants with at least 1 ATA result (negative, positive, or inconclusive) postbaseline. |

## 9.4 STATISTICAL ANALYSES

The first version of the statistical analysis plan (SAP) has been developed according to the initial version of the protocol (original protocol dated 26 February 2020) and approved before the first participant was randomized in Part A. The SAP will be updated to reflect the protocol amendments and finalized before the primary safety endpoints analysis (DLT). It will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

### 9.4.1 General considerations

Efficacy analyses (ORR and DCR for all parts, DOR and PFS for Parts A and C as per RECIST 1.1) will be performed on the all-treated population bypart, by DL, and overall. Objective response rates will be derived using the local radiologist's/Investigator's assessment.

The study cut-off for ORR (primary efficacy endpoint analysis) corresponds to the date on which all treated participants have had at least 2 postbaseline tumor assessments, experienced confirmed objective response, or have discontinued the study for any reason. This study cut-off will occur by part (Parts A & C) upon completion of enrollment at a given DL (unless cut-off dates for DLs are close) and will be approximately 4.5 months after the date of the first IMP administration of the last participant in each part: 3 months for 2 tumor assessments and 1.5 months if a confirmation of response is needed. The DCR will also be assessed at this cut-off.

For Part A and Part C, an interim analysis will be performed when the first 10 participants treated at the lower DL (100 mg/m$^2$) have had at least 2 postbaseline tumor assessments, experienced confirmed objective response, or have discontinued the study for any reason. The interim analysis is anticipated to occur approximately 4.5 months (3 months for 2 tumor assessments, and 1.5 months to permit confirmation of a response) after the date of the first IMP administration of the tenth participant in each part.

The study cut-off for the secondary efficacy endpoints (DOR and PFS) will be performed 6 months after the data cut-off date for ORR. At that time, the primary analysis of ORR and DCR will also be updated.

All safety analyses will be performed on the all-treated population, by part, by DL and overall. For each safety parameter, a baseline value will be defined as the latest value or measurement taken up to the first administration of the IMP.

In addition, for Parts B and C, select endpoints (such as ORR and key safety analyses) will be summarized by combination arm (carboplatin or cisplatin) separately.

The observation period will be divided into 4 segments:

- The pretreatment period is defined as the period up to first IMP administration.
  - The prescreening period is defined as the time from when the participants give prescreening informed consent to the day before the screening informed consent.
  - The screening period is defined as the time from when the participants give screening informed consent to the first administration of 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 end of the treatment period.

### 9.4.2 Primary endpoint

There are 2 primary endpoints: incidence of DLTs at Cycle 1 and ORR per RECIST 1.1 for Parts A and C.

#### *9.4.2.1 Incidence of DLTs at Cycle 1*

The primary safety endpoint is the incidence of study drug-related DLTs at Cycle 1 (C1D1 to C1D21). DLT includes but is not limited to corneal toxicity.

DLTs observed during the DLT observation period (Cycle 1) will be summarized on the DLT-evaluable population, by part, DL, and overall (if applicable). In addition, AEs that meet the DLT criteria in subsequent cycles will be summarized on the all-treated population. Details will be provided for each participant.

#### *9.4.2.2 Objective response rate (RECIST)*

The primary efficacy endpoint is the ORR. The ORR will be estimated, by dividing the number of participants with confirmed objective response (CR or PR as BOR), determined according to RECIST 1.1, by the number of participants from the analysis population.

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

Objective response rate will be summarized on the all-treated population by part, DL, and overall using descriptive statistics. In addition, 2-sided 95% CIs will be computed using the Clopper-Pearson method.

### 9.4.3 Secondary endpoints

Secondary endpoints include DOR and DCR for all parts, PFS for Parts A and C, and ORR for Part B per RECIST 1.1, safety, immunogenicity, and PK. Analyses of ORR for Part B will be similar to those for Parts A and C.

#### *9.4.3.1 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 anticancer therapy or death due to any cause.

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

#### *9.4.3.2 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 before the cut-off date prior to the initiation of a further anticancer therapy, then PFS will be censored at the date of the last valid tumor assessment performed before the date of initiation of a further anticancer 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.

#### *9.4.3.3 Disease control rate*

The disease control rate (DCR) 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 in the all-treated population with descriptive statistics. In addition, 2-sided 95% CIs will be computed using the Clopper-Pearson method.

#### *9.4.3.4 Adverse events*

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

- Pretreatment AEs are defined as AEs occurring during the pretreatment 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. Pretreatment and posttreatment 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 permanent treatment discontinuation
- Treatment-related TEAEs
- Treatment-related TEAEs Grade ≥3
- Serious treatment-related TEAEs
- Adverse events of special interest (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 premature discontinuation, TEAEs leading to permanent 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.

#### *9.4.3.5 Deaths*

The following deaths summaries will be generated:

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

#### *9.4.3.6 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 abnormalities (out of normal range laboratory values) will be displayed.

#### *9.4.3.7 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.

#### *9.4.3.8 Pharmacokinetic variables*

Pharmacokinetic analysis will be described in the SAP.

The population PK and PK/PD analyses will be described and reported separately.

### 9.4.4 Other analyses

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

At the end of the safety run-in, the occurrence of DLT and other safety data will be reviewed by the Study Committee to determine the RDE.

For Parts A and Part C, an interim analysis will be performed for the lower DL (100 mg/m$^2$) based on the number of confirmed objective responses observed in 10 participants treated at this DL. The study cut-off date for the interim analysis in each part corresponds to the date on which 10 treated participants have had at least 2 postbaseline tumor assessments, experienced confirmed objective response, or have discontinued the study for any reason. For participants with 2 postbaseline tumor assessments and occurrence of response at the second postbaseline tumor assessment, the confirmatory assessment will also be included.

For Part A, if fewer than 3 objective responses are observed among 10 treated participants, enrollment at this DL will be stopped. For Part C, if fewer than 4 confirmed objective responses are observed among 10 treated participants, the enrollment at this DL will be stopped. If enrollment at the lower DL (100 mg/m$^2$) is stopped early, at least 20 participants will be treated at an intermediate DL (120 mg/m$^2$). Otherwise, the enrollment will continue with 10 additional participants at the 100 mg/m$^2$ DL to total at least 20 participants. An optional 10 participants may be treated at an additional DL determined by several factors including PK modeling, safety, and efficacy of the RDE and lower DL cohorts. The statistical analysis plan will describe the planned interim analyses in greater detail.

In addition, to support project strategic planning and design of future studies, informal interim analysis may be conducted during the study.

## 9.6 DATA MONITORING COMMITTEE (DMC) OR OTHER REVIEW BOARD

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
  - The General Data Protection Regulation (GDPR) and any other applicable data protection laws
  - Any other applicable laws and regulation
- 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, as applicable:
  - 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
  - sDetermining whether an incidental finding (as per Sanofi policy) should be returned to a participant and, if it meets the appropriate criteria, to ensure the finding is returned (an incidental finding is a previously undiagnosed medical condition that is discovered unintentionally and is unrelated to the aims of the study for which the tests are being performed). The following should be considered when determining the return of an incidental finding:
    1. The return of such information to the study participant (and/or his/her designated healthcare professional, if so designated by the participant) is consistent with all applicable national, state, or regional laws and regulations in the country where the study is being conducted, and

2. The finding reveals a substantial risk of a serious health condition or has reproductive importance, AND has analytical validity, AND has clinical validity.
3. The participant in a clinical study has the right to opt out of being notified by the Investigator of such incidental findings. In the event that the participant has opted out of being notified and the finding has consequences for other individuals, eg, the finding relates to a communicable disease, Investigators should seek independent ethical advice before determining next steps.
4. In case the participant has decided to opt out, the Investigator must record in the site medical files that she/he does not want to know about such findings.

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

### 10.1.2 Informed consent process

- The Investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant.
- 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 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 will be rescreened after this period screen failed and then rescreen need to re-sign a new screening ICF, here will be no re-prescreening for CEACAM5 expression, and the initial value will be applicable within the maximum allowed window for prescreening.
- The ICF will contain separate sections that address the use of biological samples and data for Future Research and the use of the optional blood sample for CEACAM5 expression assessment on CTCs.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 11 (Section 10.1.1).

### 10.1.3 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 (General Data Protection Regulation). The study Sponsor is the Sanofi company responsible for ensuring compliance with this matter, when processing data from any individual who may be included in the Sanofi databases, including trial participants, Investigators, nurses, experts, service providers, Ethics Committee members, etc.

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

**Protection of participant personal data**

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

Participant race and ethnicity will be collected in this study because these data are required by regulatory agencies (eg, on African-American population for the FDA or on Japanese population for the Pharmaceuticals and Medical Devices Agency in Japan).

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

Participants must be informed that their 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 as described in the informed consent.

Participants must be informed that their 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.

**Protection of personal data related to professionals involved in the study**

- Personal data (eg, contact details, affiliation(s) details, job title and related professional information, role in the study, professional resume, training records) are necessary to allow Sanofi to manage involvement in the study and/or the related contractual or pre-contractual relationship. They may be communicated to any company of the Sanofi group ("Sanofi") or to Sanofi service providers, where needed.
- Personal data can be processed for other studies and projects. At any time, objection to processing can be made by contacting the Sanofi Data Protection Officer (link available at Sanofi.com).

- In case of refusal to the processing of personal data by or on behalf of Sanofi, it will be impossible to involve the professionals in any Sanofi study. In case the professionals have already been involved in a Sanofi study, they will not be able to object to the processing of their personal data as long as they are required to be processed by applicable regulations. The same rule applies in case the professionals are listed on a regulatory agencies disqualification list.
- Personal data can be communicated to the following recipients:
  - Personnel within Sanofi or partners or service providers involved in the study
  - Judicial, administrative and regulatory authorities, in order to comply with legal or regulatory requirements and/or to respond to specific requests or orders in the framework of judicial or administrative procedures. Contact details and identity may also be published on public websites in the interest of scientific research transparency
- Personal data may be transferred towards entities located outside the Economic European Area, in countries where the legislation does not necessarily offer the same level of data protection or in countries not recognized by the European Commission as offering an adequate level of protection. Those transfers are safeguarded by Sanofi in accordance with the requirement of European law including, notably:
  - The standard contractual clauses of the European Commission for transfers towards our partners and service providers,
  - Sanofi's Binding Corporate Rules for intra-group transfers.
- Professionals have the possibility to lodge a complaint with Sanofi leading Supervisory Authority, the "Commission Nationale de l'Informatique et des Libertés" (CNIL) or with any competent local regulatory authority.
- Personal data of professionals will be retained by Sanofi for up to thirty (30) years, unless further retention is required by applicable regulations.
- In order to facilitate the maintenance of Investigators personal data, especially if they contribute to studies sponsored by several pharmaceuticals companies, Sanofi participates in the Shared Investigator Platform (SIP) and in the TransCelerate Investigator Registry (IR) project (https://transceleratebiopharmainc.com/initiatives/investigator-registry). Therefore, personal data will be securely shared by Sanofi with other pharmaceutical company members of the TransCelerate project. This sharing allows Investigators to keep their data up-to-date once for all across pharmaceutical companies participating in the project, with the right to object to the transfer of the data to the TransCelerate project.
- Professionals have the right to request the access to and the rectification of their personal data, as well as their erasure (where applicable) by contacting the Sanofi Data Protection Officer: Sanofi DPO - 54 rue La Boétie - 75008 PARIS - France (to contact Sanofi by e-mail, visit https://www.sanofi.com/en/our-responsibility/sanofi-global-privacy-policy/contact).

Participant data are intended to be used for the whole drug development program from collection to reimbursement.

### 10.1.4 Committees structure

Composition of the Study Committee will vary based on the matter discussed, however it will generally include sponsor representatives and at least 2 investigators with participants. Sponsor representatives and Investigators will review clinical data approximately every 2 weeks during the study. The dosage decision for the doublet combination, triplet combinations and quadruplet combinations will be made during this meeting.

There is no Data Monitoring Committee (DMC) or Independent Radiological review committee (IRC) in this study.

### 10.1.5 Dissemination of clinical study data and results

At the end of the clinical study, the Sponsor may publish the study results in scientific journal(s). As part of the review for publication, independent scientists may need to use “coded” data of all the study participants to independently verify the study’s results.

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, euclinicaltrials.eu, and sanofi.com, as well as some national registries. For pediatric and adult trials, the results will generally be submitted/released 6 and 12 months respectively, after the end of the clinical trial worldwide (ie, the last active, participating country).

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

Individual anonymized participant data and supporting clinical documents are available for request at vivli.org. While making information available we continue to protect the privacy of participants in our clinical trials. Details on data sharing criteria and process for requesting access can be found at this web address: https//vivli.org.

### 10.1.6 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.

### 10.1.7 Source documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Every data point recorded in the CRF must have a source document. 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 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.

### 10.1.8 Study and site start and closure

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

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

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

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

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

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

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

### 10.1.9 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 9 will be performed by the local laboratory with the exception of CEACAM5, which will be performed in the central laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

- Pregnancy testing (urine or serum as required by local regulations) should be conducted every 3 weeks before each IMP administration.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted at least 30 days after the end of relevant systemic exposure corresponding with the time frame for female participant contraception in Section 5.1.
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.

**Table 9 - Protocol-required laboratory assessments**

| Laboratory assessments | Parameters |
|---|---|
| Hematology | |
| | Platelet count |
| | Hemoglobin |
| | Hematocrit |
| | White blood cell (WBC) count with differential: |
| | Neutrophils[a] |
| | Lymphocytes |
| | Monocytes |
| | Eosinophils |
| | Basophils |
| Coagulation | International normalized ratio (INR) |
| Clinical chemistry[b] | |
| | Blood urea nitrogen (BUN) or urea |
| | Creatinine |
| | Potassium |
| | Sodium |
| | Calcium |
| | Phosphate |
| | Chloride |
| | Aspartate aminotransferase (AST)/Serum glutamic-oxaloacetic transaminase (SGOT) |
| | Alanine aminotransferase (ALT)/Serum glutamic-pyruvic transaminase (SGPT) |
| | Alkaline phosphatase |
| | Total and conjugated bilirubin |
| | Glucose |
| | Lactate dehydrogenase (LDH) |
| | Albumin |
| | Total protein |
| | Circulating carcinoembryonic antigen (CEA) |
| Thyroid function | Thyroid-stimulating hormone (TSH) |
| | Total tri-iodothyronine (T3) [c] |
| | Free thyroxine (FT4) |

| Laboratory assessments | Parameters |
|---|---|
| Other screening tests | • Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only)<br>• Highly sensitive serum or urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential) [d]<br>• Serology (HIV antibody if required, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody)<br>• The results of each test must be entered into the CRF. |

NOTES:

*a* If Grade 4 neutropenia, assess ANC every 2-3 days until ANC ≥0.5 x $10^9$/L

*b* Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 8.3.11.5. All events of ≥ Grade 3 ALT/AST increase must be reported as an AESI. Investigators must document their review of each laboratory safety report.

*c* Total T3 is preferred; if not available free T3 may be tested

*d* Serum pregnancy test will be performed at screening and end of treatment. If required to repeat during treatment period, local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

Investigators must document their review of each laboratory safety report.

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

### 10.3.1 Definition of AE

**AE definition**

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

**Events meeting the AE definition**

- Any abnormal laboratory test results (hematology, 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), or more severe than expected for the participant's condition), eg:
  - Leading to IMP discontinuation or modification of dosing, and/or
  - Fulfilling a seriousness criterion, and/or
  - Defined as an AESI
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

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

**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 CRF.
- 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 CRF page.
- There may be instances when copies of medical records for certain cases are requested by Sanofi. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to 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 intensity categories according to NCI-CTCAE v.5.0.

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

**Assessment of causality**

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to Sanofi. However, **it is very important that the Investigator always makes 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.

- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally 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 Sanofi 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: CONTRACEPTIVE GUIDANCE AND COLLECTION OF PREGNANCY INFORMATION

**DEFINITIONS:**

**Woman of childbearing potential (WOCBP)**

A woman is considered fertile following menarche and until becoming postmenopausal 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

- Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)[c]
- 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

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c]
  - oral
  - intravaginal
  - transdermal
  - injectable
- Progestogen-only hormone contraception associated with inhibition of ovulation[c]
  - oral
  - injectable
- Sexual abstinence

  (Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)

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

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

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

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

## 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. 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. The initial 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. 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 for medical reasons 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 8.3.4. 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.

## 10.5 APPENDIX 5: GENETICS

### Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.
- DNA/RNA samples will be used for research related to tusamitamab ravtansine or nonsquamous NSCLC and related diseases. They may also be used to develop tests/assays including diagnostic tests related to CEACAM5 targeting drug and NSQ NSCLC. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome (as appropriate).
- DNA samples will be analyzed for determination of tumor mutation profile on plasma cfDNA. Subtractive mutation analysis will be performed with germline DNA data to identify tumor specific somatic genetic aberrations.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to tusamitamab ravtansine or study interventions of this class to understand study disease or related conditions.
- The results of genetic analyses may be reported in the clinical study report (CSR) or in a separate study summary.
- The Sponsor will store the DNA/RNA samples in a secure storage space with adequate measures to protect confidentiality.

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

**Table 10 - Recommended dose modification or discontinuation for tusamitamab ravtansine**

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

| Event | Symptoms severity (NCI CTCAE v5) | Dose modification | Supportive care guidelines |
|---|---|---|---|
| Conduction disorder associated with tusamitamab ravtansine | Grade 1<br>Mild symptoms | 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.<br>Additional evaluations such as LVEF and Holter monitoring should be performed when relevant. |
| | Grade ≥2 | Permanent discontinuation of tusamitamab ravtansine. | ECG to be repeated twice weekly until event resolution.<br>Prompt cardiology consultation<br>Additional evaluations such LVEF and Holter monitoring should be performed when relevant. |
| Neutrophil count decreased | Grade 1<br><LLN - 1500/$mm^3$; <LLN - 1.5 × $10^9$/L | No change in IMPs administration. | No intervention. |
| | Grade 2<br><1500 - 1000/$mm^3$; <1.5 - 1.0 × $10^9$/L | Delay the cycle until recovery of absolute neutrophil count >1500/$mm^3$.<br>Restart at the same dose. | No intervention. |
| | Grade 3<br><1000 - 500/$mm^3$; <1.0 - 0.5 × $10^9$/L<br>Or<br>Grade 4<br><500/$mm^3$; <0.5 × $10^9$/L | Delay the cycle.<br>Restart the treatment when absolute neutrophil count >1500/$mm^3$ at the same dose.<br>Prophylactic G-CSF can be considered in all subsequent cycle | Follow ASCO guidelines on usage G-CSF and antibiotherapy (18).<br>Repeat the test every 3 days. |
| | Grade 4 >7days<br><500/$mm^3$; <0.5 × $10^9$/L | Delay the cycle until absolute neutrophil count >1500/$mm^3$.<br>1st episode: administer next cycle at the same dose and administer growth factors<br>2nd episode: administer tusamitamab ravtansine at reduced dose<br>3rd episode: permanent discontinuation | Follow ASCO guidelines on usage G-CSF and antibiotherapy (18).<br>Repeat the test every 3 days. |
| Febrile neutropenia | Grade 3<br>Absolute neutrophil count <1000/$mm^3$ with a single temperature of >38.3°C (101°F) or a sustained temperature of ≥38°C (100.4°F) for more than 1 hour | Delay cycle until absolute neutrophil count >1500/$mm^3$.<br>1st episode: administer next cycle at the same dose and administer G-CSF<br>2nd episode: administer tusamitamab ravtansine at reduced dose<br>3rd episode: permanent discontinuation | To ensure relative dose intensity, G-CSF is recommended as secondary prophylaxis in all patients with Grade ≥3 febrile neutropenia<br>ASCO guideline is recommended for supportive treatment if there are no defined clinical standards (18). |

| Event | Symptoms severity (NCI CTCAE v5) | Dose modification | Supportive care guidelines |
|---|---|---|---|
| | Grade 4<br>Life-threatening consequences | Administration changes to be decided at the Investigator's discretion.<br>1st episode: administer next cycle at reduced dose and administer G-CSF or permanently discontinue<br>2nd episode: permanent discontinuation | |
| Hepatic enzyme increase | Grade 1-2 | Administer tusamitamab ravtansine as planned. | No intervention. |
| | Grade 3 | 1st episode: Delay the cycle. Restart the treatment until recovery to Grade 1.<br>2nd episode: Delay the cycle. Restart the treatment until recovery to Grade 1 and restart at reduced dose.<br>3rd Episode: permanent discontinuation | Additional liver function tests will be done every 2-3 days until recovery to baseline value. |
| | Grade 4 | Tusamitamab ravtansine should be permanently discontinued. | Additional liver function tests will be done every 2-3 days until recovery to baseline value. |
| Peripheral neuropathy | Grade 1<br>Asymptomatic | No action | Patient who has ongoing Grade 1 neuropathy has high risk of worsening of his/her symptoms and should be closely followed. |
| | Grade 2<br>Moderate symptoms; limiting instrumental Activities of Daily Living | Delay cycle, dose reduction if no improvement with dose delay | |
| | Grade 3<br>Severe symptoms; limiting self care Activities of Daily Living | Permanent discontinuation | |
| | Grade 4<br>Life-threatening consequences; urgent | Permanent discontinuation | |
| Hemorrhage | Grade 3 or 4 | Permanently discontinue tusamitamab ravtansine | |

*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.

**Table 11 - Recommended dose modification or discontinuation for pembrolizumab**

| Event | Symptoms severity (NCI CTCAE v4) | Dose modification |
|---|---|---|
| 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<br>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.

**Table 12 - Recommended dose modification for cisplatin/carboplatin and pemetrexed hematological toxicity**

| Platelets | ANC | Pemetrexed | Cisplatin/Carboplatin |
|---|---|---|---|
| ≥50 × $10^9$/L AND | ≥0.5 × $10^9$/L | No dose modification | No dose modification |
| ≥50 × $10^9$/L AND | <0.5 × $10^9$/L | Dose reduction by 1 level | Dose reduction by 1 level |
| <50 × $10^9$/L without bleeding AND | ANY | Dose reduction by 1 level | Dose reduction by 1 level |
| <50 × $10^9$/L with Grade ≥2 bleeding AND | ANY | Dose reduction by 2 levels | Dose reduction by 2 levels |
| ANY AND | <1 × $10^9$/L + fever ≥38.5°C | Dose reduction by 1 level | Dose reduction by 1 level |

**Table 13 - Recommended dose modification for cisplatin/carboplatin and pemetrexed nonhematological toxicity**

| | | Pemetrexed | Cisplatin | Carboplatin |
|---|---|---|---|---|
| Events | CTC Grade | Dose adjustment | | |
| Nausea or vomiting | Grade 3 or 4 | No dose modification | No dose modification | No dose modification |
| Diarrhea | Grade 3 or 4 | Dose reduction by 1 level | Dose reduction by 1 level | No dose modification |
| Mucositis | Grade 3 or 4 | Dose reduction by 2 levels | No dose modification | No dose modification |
| Neurotoxicity | Grade 2 | No dose modification | Dose reduction by 2 levels | No dose modification |
| | Grade 3 or 4 | Dose reduction by 1 level | Discontinue | Dose reduction by 1 level |
| Transaminase elevation | Grade 3 | Dose reduction by 1 level | Dose reduction by 1 level | Dose reduction by 1 level |
| | Grade 4 | Discontinue | Discontinue | Discontinue |
| Other nonhematological toxicity | Grade 3 or 4 | Dose reduction by 1 level | Dose reduction by 1 level | Dose reduction by 1 level |

## 10.7 APPENDIX 7: COUNTRY-SPECIFIC/REGION REQUIREMENTS

Serology for HBsAg and HCV and HIV test at screening will be performed only if required at the country level, such as Czech Republic.

## 10.8 APPENDIX 8: STRONG CYP3A INHIBITORS

**Table 14 - List of strong CYP3A inhibitors**

| STRONG CYP3A INHIBITORS | | | |
|---|---|---|---|
| **CYP3A inhibitors** | **Precipitant Therapeutic Class** | **Victim (oral, unless otherwise specified)** | **AUC Ratio** |
| **Potent CYP3A Inhibitors (yielding substrate AUC ratio >5)** | | | |
| VIEKIRA PAK | Antivirals | Tacrolimus | 55.76 |
| Telaprevir | Antivirals | Midazolam | 13.5 |
| Indinavir/RIT | Protease inhibitors | Alfentanil | 36.50 |
| Tipranavir/RIT | Protease inhibitors | Midazolam | 26.91 |
| Ritonavir | Protease inhibitors | Midazolam | 26.41 |
| Cobicistat | Pharmacokinetic Enhancer | Midazolam | 19.03 |
| Indinavir | Protease inhibitors | Midazolam | 9.67 |
| Ketoconazole | Antifungals | Midazolam | 17.08 |
| Troleandomycin | Antibiotics | Midazolam | 14.80 |
| Saquinavir/RIT | Protease inhibitors | Midazolam | 12.48 |
| Itraconazole | Antifungals | Midazolam | 10.80 |
| Voriconazole | Antifungals | Midazolam | 9.63 |
| Mibefradil | Calcium Channel Blockers | Midazolam | 8.86 |
| Clarithromycin | Antibiotics | Midazolam | 8.39 |
| Danoprevir/RIT | Antivirals | Midazolam | 13.42 |
| Lopinavir/RIT | Protease inhibitors | Alfentanil | 11.47 |
| Elvitegravir/RIT | Treatments of AIDS | Midazolam | 12.8 |
| Posaconazole | Antifungals | Midazolam | 6.23 |
| Telithromycin | Antibiotics | Midazolam | 6.2 |
| Conivaptan | Vasopressin antagonists | Midazolam | 5.76 |
| Nefazodone | Antidepressants | Midazolam | 5.44 |
| Nelfinavir | Protease inhibitors | Midazolam | 5.29 |
| Saquinavir | Protease inhibitors | Midazolam | 5.18 |
| Boceprevir | Antivirals | Midazolam | 5.05 |
| Idelalisib | Kinase inhibitors | Midazolam | 5.15 |
| LCL161 | Cancer treatments | Midazolam | 8.80 |
| Mifepristone | Antiprogestins | Simvastatin | 10.40 |
| Ceritinib | Kinase Inhibitors | Midazolam | 5.42 |
| Ribociclib | Kinase Inhibitors | Midazolam | 5.17 |
| Josamycin | Antibiotics | Ivabradine | 7.70 |

| STRONG CYP3A INHIBITORS | | | |
|---|---|---|---|
| **CYP3A inhibitors** | **Precipitant Therapeutic Class** | **Victim (oral, unless otherwise specified)** | **AUC Ratio** |
| **Potent CYP3A Inhibitors (yielding substrate AUC ratio >5)** | | | |
| Tucatinib | Kinase Inhibitors | Midazolam | 5.74 |
| Lonafarnib | Other | Midazolam | 7.39 |

List extracted from the Drug Interaction Database from the University of Washington (Home Page: www.druginteractioninfo.org; https://didb.druginteractionsolutions.org/resources/list-of-substrates-inhibitors-and-inducers/?Oid=1130), updated in October 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.

## 10.9 APPENDIX 9: RESPONSE EVALUATION CRITERIA IN SOLID TUMORS VERSION 1.1

Details provided in bibliographic reference (2).

### 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 truly non-measurable lesions. Lesions considered non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, 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**:
  1. Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
  2. 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.
- **Lesions with prior local treatment:**
  1. Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

**Method of assessment**

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

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

- **Clinical lesions:** Clinical lesions will only be considered measurable when they are superficial and ≥10 mm diameter as assessed using calipers. For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may be reviewed at the end of the study.
- **Chest X-ray:** Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

- **CT, MRI:** CT is the best currently available and reproducible method to measure lesions selected for response assessment. Measurability of lesions on CT scan is based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.
- **Ultrasound:** Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.
- **Endoscopy, laparoscopy:** The utilization of these techniques for objective tumor evaluation is not advised.
- **Tumor markers:** Tumor markers alone cannot be used to assess objective tumor response.
- **Cytology, histology:** These techniques can be used to differentiate between PR and CR in rare cases if required by protocol.

**Baseline documentation of 'target' and 'non-target' lesions**

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

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

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

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

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

### Response criteria

Response criteria are described in Table 15.

**Table 15 - 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.
- Progressive Disease: Unequivocal progression of existing non-target lesions. (Note: the appearance of 1 or more new lesions is also considered progression).

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

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

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

**New lesions**

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

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the 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:

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

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

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

**Evaluation of best overall response**

Time point response: At each protocol specified time point, a response assessment should occur. Table 16 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

**Table 16 - 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 17 is to be used.

**Table 17 - Response in patients with non-target disease only**

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

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

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

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

**Special notes on response assessment**

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

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

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

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

**Duration of response**

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

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

**Duration of stable disease**

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

Reproduced from: Eisenhauer EA, Therasse P, Bogaerts J et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228-47.(2)

## 10.10 APPENDIX 10: MASCC CORTICOSTEROID DOSING GUIDELINES (2016 GUIDELINES)

**Table 18 - Recommended corticosteroid (dexamethasone) dosing**

| Dexamethasone[a] | | Dose and Schedule |
|---|---|---|
| High Risk | Acute Emesis | 20 mg once<br>(12 mg when used with [fos] aprepitant or netupitant)[b] |
| | Delayed Emesis | 8 mg bid for 3 - 4 days<br>(8 mg once daily when used with (fos)aprepitant or netupitant) |
| Moderate Risk | Acute Emesis | 8 mg once |
| | Delayed Emesis | 8 mg daily for 2 - 3 days<br>(many panelists give the dose as 4 mg bid) |
| Low Risk | Acute Emesis | 4 - 8 mg once |

*a* While corticosteroids other than dexamethasone are effective antiemetics, the dose and schedule of dexamethasone coupled with its wide availability in various dose forms established it as the guideline agent of choice.

*b* The 12 mg dose of dexamethasone is the only one tested with (fos)aprepitant/netupitant in large randomized trials.

## 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 the COVID-19 pandemic.

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

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

Contingency procedures to ensure the safety of the participants, to protect trial integrity, to maintain continuity of study conduct, and to support compliance with GCP in Conduct of Clinical Trials Guidance for an emergency that prevents access to the study site are suggested below and in Section 5.5, Section 7.1.2, Section 8, Section 9.4.4, and Section 10.1.2. The agreement of the Sponsor MUST be obtained prior to the implementation of these procedures for the duration of the emergency.

During the emergency, if the site will be unable to adequately follow protocol-mandated procedures, alternative treatment outside the clinical trial should be proposed, and screening/enrollment/administration of study intervention may be temporarily delayed/halted (see also Section 5.5). Attempts should be made to perform all assessments in accordance with the approved protocol to the extent possible. In case this is not possible due to a temporary disruption caused by an emergency, focus should be given to assessments necessary to ensure the safety of participants and those important to preserving the main scientific value of the study. Contingencies implemented due to emergency will be documented.

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 CEACAM5 expression). The Investigator/delegate should respond to any question raised by a participant, and this correspondence should be documented in detail in the participant's source file.

- If a participant agrees to participate in the prescreening phase, the participant should print out, sign, and date 2 copies of the ICF. A scan of a signed ICF should be sent via secured e-mail (if available), and 1 of the signed original ICFs to be filed in the Investigator Study File should be sent via postal mail.
- The Investigator/delegate should review each received signed ICF (or a printout of an electronically submitted, scanned copy), sign and date it, and archive it in the Investigator Study File. After properly documenting this consent process, the site may proceed to prepare and send the slides for CEACAM5 assessment. 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.

### 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 judgment and depending on the country/site status, should be communicated to the participant. The participant should satisfy all eligibility criteria before enrolling to the study; 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, reinitiation) of the IMP can occur only once the Investigator has determined, according to his/her best judgment, that the contribution of the IMP(s) to the occurrence of the epidemic event (eg, COVID-19) was unlikely.

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

### 10.11.4 Study procedures

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

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

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

Depending on site status, if needed, 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.

### 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.

### 10.11.6 Informed consent process

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

## 10.12 APPENDIX 12: ABBREVIATIONS

| | |
|---|---|
| ADC: | antibody-drug conjugate |
| AE: | adverse event |
| AESI: | adverse event of special interest |
| AIDS: | acquired immunodeficiency syndrome |
| ALK: | anaplastic lymphoma kinase |
| ALT: | alanine aminotransferase |
| ANC: | absolute neutrophil count |
| AP: | alkaline phosphatase |
| AST: | aspartate aminotransferase |
| BSA: | body surface area |
| BUN: | blood urea nitrogen |
| C: | cycle |
| CEA: | carcinoembryonic antigen |
| CEACAM5: | carcinoembryonic antigen-related cell adhesion molecule 5 |
| cfDNA: | circulating free deoxyribonucleic acid |
| CI: | confidence interval |
| CR: | complete response |
| CT: | computed tomography |
| CTLA-4: | cytotoxic T-lymphocyte-associated antigen 4 |

| | |
|---|---|
| D: | day |
| DCR: | disease control rate |
| DL: | dose level |
| DL-1: | dose level minus 1 |
| DLT: | dose-limiting toxicity |
| DNA: | deoxyribonucleic acid |
| DOR: | duration of response |
| ECG: | electrocardiogram |
| ECOG: | Eastern Cooperative Oncology Group |
| eCRF: | electronic case report form |
| eGFR: | glomelular filtration rate (estimated) |
| EGFR: | epidermal growth factor receptor |
| EOT: | end of treatment |
| FDG-PET: | fluorodeoxyglucose-positron emission tomography |
| FFPE: | formalin-fixed, paraffin embedded |
| FIH: | first-in-human |
| GCP: | Good Clinical Practice |
| HBsAg: | hepatitis B surface antigen |
| HCV: | hepatitis C virus |
| HIV: | human immunodeficiency virus |
| HNSCC: | head and neck squamous cell carcinoma |
| ICF: | informed consent form |
| ICH: | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| ICI: | immune-checkpoint inhibitor |
| IMP: | investigational medicinal product |
| INR: | international normalized ratio |
| IV: | intravenous |
| LDH: | lactate dehydrogenase |
| MDRD: | modification of diet in renal disease |
| MedDRA: | medical dictionary for regulatory activities |
| MRI: | magnetic resonance imaging |
| NE: | not evaluable |
| NSCLC: | non-small-cell lung cancer |
| NSQ: | nonsquamous |
| NSQ NSCLC: | nonsquamous, non-small-cell lung cancer |
| ORR: | objective response rate |
| OS: | overall survival |
| PD: | pharmacodynamic |
| PD-1: | programmed cell death protein 1 |
| PD-L1: | programmed death-ligand 1 |
| PD-L2: | programmed death-ligand 2 |
| PFS: | progression-free survival |
| PS: | performance status |
| PT: | preferred term |
| RECIST: | response evaluation criteria in solid tumors |

| | |
|---|---|
| RNA: | ribonucleic acid |
| SAP: | statistical anlysis plan |
| SGOT: | serum glutamic-oxaloacetic transaminase |
| SGPT: | serum glutamic-pyruvic transaminase |
| SJS: | Stevens-Johnson syndrome |
| SoA: | schedule of activities |
| SOC: | system organ class |
| TEN: | toxic epidermal necrolysis |
| TPS: | tumor proportion score |
| TSH: | thyroid-stimulating hormone |
| ULN: | upper limit of normal |
| US: | United States |
| VS: | vital signs |
| WBC: | white blood cell |
| WOCBP: | woman of childbearing potential |

### 10.13 APPENDIX 13: PROTOCOL AMENDMENT HISTORY

There have been 5 previous amendments (Amended protocol 05, 04 July 2022; Amended protocol 01, 23 November 2020; Amended protocol 02, 25 January 2021; Amended protocol 03, 04 May 2021, Amended protocol 04, 18 August 2021); these changes are summarized in this section. The Protocol Amendment Summary of Changes Table for the current amendment (Amended protocol 05) is located directly before the Table of Contents (TOC).

### Amended protocol 01 (23 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.

## OVERALL RATIONALE FOR THE AMENDMENT

This amendment is intended primarily to add a SAR408701 dose level of 170 mg/m$^2$ Q3W to be evaluated in Part A based on data from the SAR408701 170 mg/m$^2$ Q3W cohort in Study TED13751 and to add Part B of two treatment arms to evaluate the safety and anti-tumor activity of SAR408701 in combination with pembrolizumab and platinum-based chemotherapy in NSQ NSCLC patients positive for CEACAM5 (≥50%).

**Protocol amendment summary of changes table**

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Cover page and 1.1 Synopsis, Short title | CARMEN-LC05 was added. | To include study acronym. |
| OVERALL RATIONALE FOR THE AMENDMENT | Added rationales for new SAR408701 170 mg/m$^2$ Q3W cohort in Part A and 2 new treatment arms in Part B. | To explain reasons for important changes to study design. |
| 1.1 Synopsis, Objectives and endpoints; Section 3 Objectives and endpoints; 9.1 Statistical hypotheses | Added "Part A" to Part 1 and Part 2 primary objective and endpoint, and added new primary objective and endpoint for Part B; specified hypotheses for Part A and new Part B. | To clarify primary objectives and endpoints for Part A and introduce new primary objective and endpoint for new Part B. |
| 1.1 Synopsis, Section 3 Objectives and endpoints | Modified secondary safety and tolerabilty objective to include SAR408701 in combination with pembrolizumab and platinum-based chemotherapy. | To reflect addition of new Part B to study. |
| 1.1 Synopsis, Section 3 Objectives and endpoints; 8.5 Pharmacokinetics | Modified secondary PK objective and endpoints to include cisplatin and carboplatin pharmacokinetics, and added assessments. | To reflect addition of new Part B to study. |
| 1.1 Synopsis, Objectives and endpoints; Section 3 Objectives and endpoints | Modified secondary immunogenicity objective to include platinum-based chemotherapy. | To reflect addition of new Part B to study. |
| 1.1 Synopsis, Objectives and endpoints; Section 3 Objectives and endpoints | Added new secondary objective to include antitumor activity of SAR408701 administered with pembrolizumab and with pembrolizumab combined with platinum-based chemotherapy. | To reflect addition of new Part B to study. |
| 1.1 Synopsis, Objectives and endpoints; Section 3 Objectives and endpoints | Added secondary endpoint of objective response rate in participants treated with pembrolizumab and platinum-based chemotherapy. | To reflect addition of new Part B to study. |
| Section 3 Objectives and endpoints | Modified tertiary/exploratory objective of circulating CEA evaluation to include CEA assessments at prescreening, and specified endpoint at prescreening, screening, and during the treatment period. | To reflect addition of new prescreening time point for assessment of circulating CEA. |
| 1.1 Synopsis, Overall design; 4.3 Justification for dose; 6.1 Study interventions; 6.6.1 Determination of recommended doses (Part 1 and Part B); 6.6.2 Individual dose modification (Part A and Part B) | The dose level of SAR408701 170 mg/m$^2$ was added. | Based on the results of TED13751 study, the recommended dose of SAR408701 can be 170 mg/m$^2$ Q3W. |
| 1.1 Synopsis, Overall design; 9.2 Sample size determination | Updated planned numbers of participants in Part A and added numbers of participants planned for Part B. | To update estimates of numbers of participants to be enrolled based on addition of new doses and study arms. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.1 Synopsis, Figure 1 | Modified decision tree for SAR408701 dose selection was moved to synopsis and specified both for Part 1 of Part A and for Part B. | To clarify that it applies to both Part A and Part B of the study. |
| 1.1 Synopsis, Overall design; 1.3 Schedule of activities; 8.1 Efficacy assessments | specified timing of tumor assessments after End of Treatment visit as every 12 weeks (±7 days) after the last tumor assessment. | To clarify scheduling of tumor assessments for participants who discontinue study treatment. |
| 1.2 Schema | Original study schema labeled Part A; new schema added for Part B. | To accommodate addition of Part B to the study. |
| 1.3 Schedule of activities (SoA) | Correction of “PD-L1 positivity” to “PD-L1 Expression”. | For clarity. |
| 1.3 Schedule of activities (SoA) | “Correction of Randomization/allocation” to “Randomization (Part A)”. | For clarity. |
| 1.3 Schedule of activities (SoA); 8.2.6 Clinical safety laboratory assessements | Hematology, Liver function tests. | Hematology and liver function tests will be repeated during first 2 cycles of Part 2 to monitor the safety of SAR408701 treatment. |
| 1.3 Schedule of activities (SoA); 10.2 Appendix 2 | Glucose assessment was added. | Glucose is part of blood chemistry test. |
| 1.3.2.2 PK/ATA flow chart for Part B | New table added. | To reflect PK analysis of new arms of triplet combination treatment. |
| 4.1 Overall design | Part B was added to the overall study design. | To reflect new arms of triplet combination treatment. |
| 4.3 Justification for dose | Rationale of SAR408701 170 mg/m$^2$ Q3W was added. | Based on the results of TED13751 study, the recommended dose of SAR408701 can be 170 mg/m$^2$ Q3W. |
| 4.4 End of study definition | Specified estimated study cut-off date at 10 months after the last participant’s randomization in Part A”. | For clarity. |
| 5.1 Inclusion criteria, I04 | 5 slides required instead of 7. | CEACAM5 IHC requirement changed. |
| 5.1 Inclusion criteria, I05 | For participants enrolled to Part A added. | Only applicable to Part A. |
| 5.1 Inclusion criteria, I08 | required contraception for at least 6 months after the last dose of platinum-based chemotherapy. | In accordance with male contraception guidance for platinum-based chemotherapy. |
| 5.2 Exclusion criteria, E11 | Specified required resolution of toxicity of prior therapy to CTCAE Grade <2, rather than to Grade 2. | For clarity. |
| 5.2 Exclusion criteria, E19 | Specified that required washout period for prior treatment is the shorter of 3 weeks or 5 × half life. | For clarity. |
| 5.4 screen failures | Procedure for screen failures modified such that rescreened participants are to be assigned a different participant number from that issued for the initial screening, rather than the same number, as originally specified. | According to FDA guidance, a different participant number should be assigned to the rescreened participant. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 5.5 Criteria for temporary delaying enrollment | Section updated to include details of guidance in case of regional or national emergency; link to new Appendix 11. | As guidance for standardization across studies. |
| 6.1 Study interventions administered | Cisplatin and carboplatin added to the interventions. | To reflect new arms of triplet combination treatment. |
| 6.6.1 Determination of recommended dose | The dose level of SAR408701 170 mg/m$^2$ was added. | Based on the results of TED13751 study, the recommended dose of SAR408701 can be 170 mg/m$^2$ Q3W. |
| 6.6.2 Individual dose modification (Part 1 and Part 2) | Specified that dose is permanently reduced after a dose reduction. | For clarity. |
| 7.1.1 Definitive discontinuation | Added pregnancy to list of reasons study intervention should be discontinued. | For clarity, in keeping with requirement to discontinue in case of participant pregnancy. |
| 7.1.2 Temporary discontinuation | Section updated to include details of guidance in case of regional or national emergency; link to new Appendix 11. | As guidance for standardization across studies. |
| 7.1.2.1 Rechallenge | Section updated to include details of guidance in case of regional or national emergency; link to new Appendix 11. | As guidance for standardization across studies. |
| 7.2 Participant discontinuation/withdrawal | “rerandomized” changed to “rerandomized/reallocated”. | Clarification regarding prohibition of re-enrollment of withdrawn participants, whether or not they are randomized. |
| 8 Study Assessments and Procedures | Section updated to include details of guidance in case of regional or national emergency; link to new Appendix 11. | As guidance for standardization across studies. |
| 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. |
| 8.3.4 Regulatory reporting requirement for SAEs | Updated with deletion of the text on reporting timelines for SUSARs. | Aligned with the internal PV guidelines. |
| 8.3.7 Disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs | The paragraph deleted. | For clarity. |
| 8.3.8 Adverse event of special interest | Added dose-limiting toxicity (DLT) to list of adverse events of special interest (AESI). | Change to reporting of DLT events. |
| 8.11 Use of biological samples and data for future research | Section added to include details of use of biological samples and data for future research. | Requirement from new protocol template. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 9.4 Statistical analyses | Section updated to include statistical analyses for Part B | To reflect new arms of triplet combination treatment. |
| 9.4.4 Study assessments and procedures | Section updated to include details of guidance in case of regional or national emergency; link to new Appendix 11. | As guidance for standardization across studies. |
| 9.5 Interim analyses | Added possible interim analysis for Part A when study cut-off for primary analysis of Part B is reached. | To permit project planning. |
| 10.1.2 Informed consent process | Updated ICF process for re-screening and use of biological samples and data. | For clarity. |
| 10.1.2 Informed consent process | Section updated to include details of guidance in case of regional or national emergency; link to new Appendix 11. | Per guidance for standardization across studies. |
| 10.1.4 Committee structure | Language modified with regard to investigators who may be included in the Study Committee. | To reflect addition of new Part B of the study. |
| 10.2 Appendix 2 | Removed CEACAM5 expression and PD-L1 expression. | For clarity. |
| 10.2 Appendix 2 | Updated footnote for pregnancy test. | For clarity. |
| 10.6 Appendix 6: Recommended supportive care and/or dose modification guidelines for drug-related adverse events | New section for managing GI toxicity. | For clarity of safety management guidelines. |
| 10.7 Appendix 7: Country-specific requirements | Mentioned Czech Republic as a specific example of a country requiring additional serological testing at screening. | Per Health Authority's request. |
| 10.11 Appendix 11 | New appendix added to detail contingency measures for a regional or national emergency. | To harmonize across sites actions taken in response to regional or national emergency. |
| Throughout | Correction of typographical errors and standardization of wording. | To increase clarity. |

### Amended protocol 02 (25 January 2021)

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

## OVERALL RATIONALE FOR THE AMENDMENT

This amendment is intended to correct the typographical errors in Table 6 and Table 13 to clarify the first and second reduced doses of carboplatin in response to toxicity, as well as recommended hematological thresholds for carboplatin/cisplatin dose reductions.

**Protocol amendment summary of changes table**

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 6.6 Dose modification, Table 5 | Staring dose updated to Initial dose. | To clarify |
| 6.6 Dose modification, Table 6 | DL 0 updated to Initial dose<br>DL -1 updated to Dose reduction level -1 (DL -1)<br>DL -2 updated to Dose reduction level -2 (DL -2) | To clarify |
| 6.6 Dose modification, Table 6 | Carboplatin dose level -1 updated from AUC 5 to AUC 3.75<br>Carboplatin dose level -2 updated from AUC 5 to AUC 2.5 | To correct typographical errors and to clarify carboplatin dose reductions in response to toxicity |
| 10.6 Appendix 6 Recommended supportive care and/or dose modification guidelines for drug-related adverse events, Table 13 | Specified recommended platelet threshold for reducing cisplatin/carboplatin to DL -1 as $<50 \times 10^9$/L; and platelet threshold for reducing to DL –2 as $<50 \times 10^9$/L with Grade ≥2 bleeding | To correct typographical errors to clarify recommended thrombocytopenia thresholds for cisplatin/carboplatin dose reduction |
| 10.6 Appendix 6 Recommended supportive care and/or dose modification guidelines for drug-related adverse events, Table 13 | Specified recommended threshold of ANC $<1 \times 10^9$/L with fever with any platelet value for reducing cisplatin/carboplatin dose level to DL -1 | To correct typographical errors to clarify recommended neutropenia threshold for dose reduction |
| 10.6 Appendix 6 Recommended supportive care and/or dose modification guidelines for drug-related adverse events, Table 13 | Updated DL 0, DL -1, and DL -2 respectively to No dose modification, Dose reduction by 1 level, and Dose reduction by 2 levels | To clarify |
| 10.6 Appendix 6 Recommended supportive care and/or dose modification guidelines for drug-related averse events (Cisplatin/Carboplatin hematological toxicity, Table 14) | Updated DL 0, DL -1, and DL --2 respectively to No dose modification, Dose reduction by 1 level, and Dose reduction by 2 levels | To clarify |

### Amended protocol 03 (04 May 2021)

This amended protocol 03 (Amendment 03) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

## OVERALL RATIONALE FOR THE AMENDMENT

The main purpose of this amendment is to remove the pembrolizumab single agent arm from Part A of this study. This is due to difficulties in enrolling participants with NSCLC expression PD-L1 TPS ≥1% to be treated, given in many investigational sites, the standard of care for patients PD-L1 TPS <50% is to combine pembrolizumab with chemotherapy. Even though in the US pembrolizumab single agent is approved for the first line treatment of patients with NSCLC expressing PD-L1 TPS ≥1%, it is challenging for investigators to enroll in Part A.

**Protocol amendment summary of changes table**

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Cover page Title, Section 1.1: Protocol title | Replaced "pembrolizumab alone" with "tusamitamab ravtansine (SAR48701) combined with pembrolizumab and platinum-based chemotherapy in patients with CEACAM5-positive" | To reflect the change:<br>• Removing pembrolizumab alone arm in Part A.<br>• Adding the platinum-based chemotherapy Part B as per protocol amendment 1. |
| | "Randomized, and PD-L1 positive" were removed from title | |
| | Added "Tusamitamab ravtansine" INN name | The approved product name was added |
| Cover page Compound number (INN/Trademark) | INN name, tusamitamab ravtansine was added | The newly approved INN name was added |
| Section 1.1:Short title | Replaced "pembrolizumab alone" with "tusamitamab ravtansine (SAR408701) in combination with pembrolizumab and platinum-based chemotherapy" | To reflect the change of study design by:<br>• Removing pembrolizumab alone arm in Part A.<br>• Adding the platinum-based chemotherapy Part B as per protocol amendment 1. |
| | Added "Tusamitamab ravtansine" product name | The approved product name was added |
| Cover page Regulatory agency identifier number(s) | Added the NCT number | The missing NCT number was added |
| Document history | "Amended Clinical Trial Protocol 03" and information was added | To reflect the change of this amended protocol |
| 1.1 Synopsis (Rationale) | "TED13751" study number added | To provide details on the ongoing Phase 1 study |
| | "and for PD-L1 (≥1%)" was removed | To reflect the change of removing the pembrolizumab alone arm |
| | "in US" was added | To clarify the first line treatment of patients with NSCLC |
| 1.1 Synopsis (Objectives and endpoints), Section 3 Objectives and endpoints | Removed objectives and endpoints of pembrolizumab single agent arm | To reflect the change of removing the pembrolizumab alone arm |
| | Removed "response evaluation criteria in solid tumors" from secondary endpoints | To maintain only the abbreviation |
| | Added: "first investigational medicinal product (IMP) administration" to the third secondary endpoint | The first IMP added since randomization was removed (only single arm in Part A) |
| 1.1 Synopsis (Overall Design), Section 4.1 Study Design | Sections were updated to remove pembrolizumab single agent arm and PD-L1 requirement for Part A | To reflect the change of removing the pembrolizumab alone arm |
| | Sample size updated | Remove pembrolizumab alone arm |
| | "During the screening phase, only participants with NSQ NSCLC determined to be CEACAM5 positive will go through protocol screening procedures. Participants will be enrolled in Part A or Part B per investigator's choice" was added | To clarify |
| | The following text was added "(±5 days) and (±7 days) | Added to be consistent with schedule of activities |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.1 Synopsis (Number of participants),<br>Section 9.2 (Sample Size Determination) | The following text was added: “Note: "Enrolled" means a participant's, or their legally acceptable representative’s, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol” | Added to be consistent with template language |
| 1.1 Synopsis (Intervention groups and duration) | The safety cut-off for primary safety endpoint analysis added | Cut-off updated to include primary safety endpoint analysis in Part A in addition to Part B |
| | The following text was removed: “except PK” | To clarify that the patients will undergo all assessments, including PK |
| | “15 minutes to”; “depending on the administration form IV or oral [15 minutes prior for IV and 1 hour prior for oral] were added | To provide detailed NIMP instructions |
| 1.1 Synopsis (Statistical considerations) | Changes made to sample size and primary population for analysis. | To reflect the change of removing the pembrolizumab alone arm |
| 1.2 Schema | Removed pembrolizumab single agent arm and PD-L1 requirement for Part A; PD-L1 TPS and footnote relating to PD-L1 TPS is removed from Figure 2 | To reflect the change of removing the pembrolizumab alone arm and PD-L1 requirement for Part A |
| 1.2 Schema | “to -10 days” is added to screening ICF in Figures 2 and 3<br>“Confirmed disease progression” added to Figure 3 | Figure updated to be consistent with Section 4.1 |
| 1.2 Schema | “DLT” abbreviation removed from Figure 3 footnote, and “NSQ NSCLC” was added | Changes made according to the figure update |
| 1.3.1 Schedule of activities (SOA) | Removed “randomization (Part A)” and “Every effort should be made to start first IMP administration within 3 working days of randomization (Part A)” | No randomization as only single arm in Part A |
| 1.3.1 Schedule of activities (SOA) | Text related to “PD-L1 (Part A)” was removed from footnotes a and b | To reflect the change of removing the pembrolizumab alone arm and PD-L1 requirement for Part A |
| 1.3.1 Schedule of activities (SOA) | Tumor assessment notes were updated to “every 12 weeks (±7 days) after the last TA until confirmed disease progression, initiation of a new anticancer treatment, death, withdrawal of participant’s consent, or study cut-off date for secondary efficacy endpoints, whichever comes first | To provide additional information to the tumor assessment |
| 1.3.2 PK/ATA flowchart | ''in combination arm for both drugs and in control arm for pembrolizumab only" was deleted | To reflect the change of removing the pembrolizumab alone arm |
| 2.1 Study rationale | “In the 64 treated patients, tusamitamab ravtansine showed encouraging anti-tumor activity associated with a response rate of 20.3% per RECIST1.1 (95% CI: 12.27%–31.71%), warranting further development of tusamitamab ravtansine to treat this patient population” was added. | Updated efficacy data of high CEACAM5 expressors with NSCLC; new data available since last protocol amendment. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 2.1 Study rationale | "considering pembrolizumab alone as calibrator arm in patients with CEACAM5 and PD-L1 positive untreated advanced/metastatic NSQ NSCLC" was removed. | To reflect the change of removing the pembrolizumab alone arm and PD-L1 requirement for Part A |
| 2.1 Study rationale | The following text was added: "untreated locally advanced/metastatic | To clarify the participant population |
| 2.1 Study rationale | "Overall" was added to the response rate | To explain the analysis |
| 2.2 Background | Information on ongoing NSCLC studies (5 ongoing clinical trials, and the phase 2 trial ACT16525) is added | To provide additional details on ongoing studies with tusamitamab ravtansine |
| 4.2 Scientific rationale for study design | Updated efficacy data of high CEACAM5 expressors with NSCLC. | New data available since last protocol amendment |
| | "Overall" was added to the response rate | To explain the analysis |
| 4.4 End of study definition | "First IMP administration" was added. | To define and clarify end of study |
| 5.1 Inclusion criteria | Original criterion I05 removed. | As the pembrolizumab single agent arm was removed, participants in Part A with any PD-L1 expression can be enrolled |
| 5.2 Exclusion criteria | Criterion E03 updated | To allow patients with untreated asymptomatic brain metastases to be enrolled |
| 5.2 Exclusion criteria | Criterion E09 was updated to replace "randomization" with first study intervention "administration." | No randomization as only single arm in Part A |
| 5.2 Exclusion criteria | "x ULN" was removed from criterion E28. | Fixed units |
| 5.5 Criteria for temporarily delaying enrollment | Randomization was updated to enrollment | No randomization as only single arm in Part A |
| 6.1 Study intervention(s) administered | In Table 2, the text "comparator" was replaced by "combination component". | To reflect the change of removing the pembrolizumab alone arm |
| Study intervention(s) administered | "Carboplatin dose should not exceed 750 mg. The dose should be calculated using the Calvert formula and CrCl should be calculated by Cockcroft-Gault equation" and footnote "b" was added to Table 2 | To provide details on the Cockcroft-Gault equation |
| Study intervention(s) administered | The following text was added to dosage levels on Table 2: "on Day 1" | To be consistent with the schedule of activities |
| Study intervention(s) administered | The following text was added:<br>"15 minutes to"; "depending on the administration form IV or oral [15 minutes prior for IV and 1 hour prior for oral]; and "If oral diphenhydramine is not available, other Histamine H1 antagonist or other form of diphenhydramine can be given per local label and clinical practice." | To provide detailed NIMP instructions |
| 6.3 Measures to minimize bias: randomization and blinding | Removed the text in this section, as it is no longer applicable | The randomization and blinding text is no longer applicable |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 6.6.2 Individual dose modification (Part A and Part B) | Second reduced doses added to Table 5 | To introduce additional reduced doses |
| 6.6.2 Individual dose modification (Part A and Part B) | The following text was removed “one”. | To clarify the dose reduction of tusamitamab ravtansine |
| 7.1.1 Definitive discontinuation | The following text was added: “Any abnormal laboratory value or ECG parameter will be immediately rechecked for confirmation (please specify, eg after 24 hours) before making a decision of permanent discontinuation of the IMP for the concerned participant.” | To maintain standard, template language |
| 8 Study assessment and procedures | “Except PK” was removed and “safety” was added | To clarify that the patients will undergo all assessments, including PK |
| 8.1 Efficacy assessments | Reference date updated | Randomization is no longer applicable |
| 8.1 Efficacy assessments | “Progressive disease” was replaced with “response” | To clarify the radiological evaluation documentation |
| 9.1 Statistical hypothesis | The following text was removed: “pembrolizumab single agent” | To reflect the change of removing the pembrolizumab alone arm |
| 9.2 Sample size determination | Text related to randomization was removed and sample size updated. | To reflect the change of removing the pembrolizumab alone arm |
| 9.3 Population for analysis | Intent to treated population for Part A was removed and all-treated population was updated as the primary population for analysis of all efficacy parameters. The screened and Activity population were also updated. | No randomization as only single arm in Part A |
| 9.4 Statistical analysis | The statistical analysis plan was updated. | The SAP will be updated to reflect the protocol amendments |
| Section 9.4.1 General Considerations | The safety cut-off for primary safety endpoint analysis added | Cut-off updated to include primary safety endpoint analysis in Part A in addition to Part B |
| | Changes made to efficacy analysis population from ITT to alltreated and to the cut-off data | To reflect the change of removing the pembrolizumab alone arm |
| 9.4.2 Primary endpoints | The following text was removed: “for each treatment arm” | To reflect the change of removing the pembrolizumab alone arm |
| | “Tumor” was replaced by “overall” and “randomization” was replaced by “first IMP administration” | To be consistent with the synopsis section |
| | “for the doublet combination arm” was added | |
| 9.4.3 Secondary endpoints | “ITT” and “by treatment arm” were removed; “all-treated” was added | To reflect the change of removing the pembrolizumab alone arm |
| 9.5 Interim analyses | Removed the text in this section, as it is no longer applicable | Cut-off for primary safety analysis in Part A and Part B added instead |
| 10.8 Appendix 8 CYP substrates with narrow therapeutic range and strong CYP3A inhibitors, Table 16 | Update list of strong CYP3A inhibitors | Drug interaction list updated |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 10.13 Appendix 13 Protocol amendment history | Amendment history was updated with Amended Protocol 2 | Updated section to include Amended Protocol 2 |
| | "Hematological" added to the rationale for amendment. | To clarify the threshold for carboplatin/cisplatin dose reductions |
| Throughout | "Randomization" was removed | No randomization as only single arm in Part A |
| Throughout | SAR408701 replaced by tusamitamab ravtansine | The approved product name was added |
| Throughout | RD replaced by RP2D | To clarify the dose |
| Throughout | Reference to Pregnancy cross-sections updated | Cross-section formatting was fixed |
| Throughout | Minor editorial, typographical error corrections and standardization of wording | For clarity |

### Amended protocol 04 (18 August 2021)

This amended protocol 04 (Amendment 04) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

## OVERALL RATIONALE FOR THE AMENDMENT

The main purpose of this amendment is to add Part C to evaluate the safety and anti-tumor activity of tusamitamab ravtansine in combination with the SOC in first line, pembrolizumab, platinum-based chemotherapy and pemetrexed in NSQ NSCLC participants with CEACAM5 high (≥50%) or moderate expression (≥1% and <50%) tumors and to move primary objective of Part A with assessment of anti-tumor activity to secondary objective, as the primary objective is to assess the tolerability of the combination and to confirm the recommended dose as for the other parts, and consequently decrease the sample size in Part A to get approximately the same number of participants treated at the recommended dose in each part.

**Protocol amendment summary of changes table**

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Cover page Title, Section: 1.1: Protocol title, Section: 1.1: Short title | Added "with or without pemetrexed" | To reflect the change of adding the combination arm of tusamitamab ravtansine with the SOC pembrolizumab, platinum-based chemotherapy and pemetrexed as Part C. |
| Section 1.1: Synopsis (Rationale), Section 2.1: Study rationale | Added rationale for Part C | To reflect the change of adding the combination arm of tusamitamab ravtansine with the SOC pembrolizumab, platinum-based chemotherapy and pemetrexed as Part C, in order to evaluate the safety of the combination |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 1.1: Synopsis (Objectives and endpoints), Section 3: Objectives and endpoints | Moved anti-tumor activity of tusamitamab ravtansine in combination with pembrolizumab from primary endpoint to secondary endpoint | To reflect the change of primary endpoint and sample size for Part A |
| | Added objectives and endpoints for Part C | To reflect the change of adding Part C |
| | Removed duration of response and progression-free survival from secondary endpoints | To reflect the change of secondary endpoints and sample size of Part A |
| | Removed exploration of efficacy parameters for immune based therapy with tusamitamab ravtansine in combination with pembrolizumab and removed ORR of Part A per iRECIST from exploratory endpoint | To reflect the change of exploratory endpoints and sample size of Part A |
| Section 1.1: Synopsis (Overall Design), Section 4.1: Study Design, 9.1: Statistical hypotheses | Added Part C details to Study Design | To reflect the change of adding Part C |
| | Removed Part 2 of Part A details and updated Figure 1 | To reflect the change of primary endpoints and sample size of Part A |
| Section 1.1: Synopsis (Number of participants), Section 9.2: (Sample Size Determination) | Updated sample size details for Part A | To reflect the change in secondary end points and Sample size of Part A |
| | Added sample size details for Part C | To reflect the change of adding Part C |
| Section 1.1: Synopsis (Intervention groups and duration) | Updated pemetrexed details (formulation, route of administration, dose regimen) to the study intervention | To reflect the change of adding the combination arm of tusamitamab ravtansine with the SOC pembrolizumab, platinum-based chemotherapy and pemetrexed as Part C |
| | Removed the text related to Part A study cut-off for secondary efficacy endpoint analysis (PFS and DOR) | To reflect the change of secondary endpoints for Part A |
| Section 1.1: Synopsis (Statistical considerations), Section 9.3: Populations for analysis, | Updated sample size calculation for Part A | To reflect the removal of Part 2 of Part A |
| | Added sample size calculation for Part C | To reflect the change of adding Part C |
| | Removed “Activity population (Part A)” definition from Main analysis populations | To reflect the removal of Part 2 of Part A |
| Section 9.4.2: Primary endpoint | Removed ORR from Primary end point analysis of Part A | To reflect the change in Primary endpoint for Part A |
| Section 9.4.3: Secondary endpoint | Removed DOR and PFS from Secondary endpoint analysis from Part A | To reflect the change in Secondary endpoint for Part A |
| Section 1.2: Schema | Updated Figure 1-Decision tree for tusamitamab ravtansine dose in Part A, Part B, and Part C | To reflect the change in removal of Part 2 of Part A |
| | Removed Part 2 in Figure 2 | To reflect the change in removal of Part 2 of Part A |
| | Added Figure 4 representing the Part C | To reflect the change of adding Part C |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 1.3: SoA and Section 8.4: Pharmacodynamic assessments | Removed Tumor assessment and Circulating CEA assessments at follow-up visit | To reflect as there is no DOR/PFS assessment |
| Section 1.3: SoA, Section 3: Objective and Endpoints and Section 8.7: Genetics | Updated the text corresponding to additional plasma sampling timepoint (at Cycle 5 Day 1) for cfDNA isolation | To assess cfDNA changes in response to treatment |
| Section 1.3.2: PK/ATA flowchart and Section 8.5: Pharmacokinetics | Removed the PK/ATA flow chart for Part 1 of Part A and updated the PK/ATA flow chart for Part B and Part C | To reflect the change in measurement of PK parameters |
| | Updated PK details pertaining to Part C | To reflect the change of adding Part C |
| Section 2.2: Background | Added ACT16432 study details | To update the list of on-going trials of tusamitamab ravtansine |
| Section 2.3.2: Benefit assessment | Added the following text" As no overlap in the safety profiles for pemetrexed and platinum chemotherapies and for tusamitamab ravtansine is anticipated and for which hematological toxicity is minimal, the addition of tusamitamab ravtansine to the SOC may lead to better efficacy with acceptable safety profile" | To clarify anticipated benefit of addition of pemetrexed |
| Section 4.2.1: Participant input into design | Updated the number of patients treated and the efficacy data in Study TED13751 | New data available since last protocol amendment |
| Section 4.2: Justification for dose | Added "pemetrexed" in the text | To reflect the change of adding the combination arm of tusamitamab ravtansine with the SOC pembrolizumab, platinum-based chemotherapy and pemetrexed as Part C |
| Section 4.4: End of Study definition | Replaced the following text "estimated at 10 months after the last participant's first IMP administration in Part A" with "estimated at 4.5 months after the last participant's first IMP administration" and added "the Follow-Up visit approximately 90 days after the last IMP administration" | To clarify |
| Section 5.1: Inclusion criteria, I04 | Updated type of participant and disease characteristics for Part C | To reflect the change in addition of Part C |
| Section 5.1: Inclusion criteria, I08 | Added contraception for at least 6 months after the last dose of pemetrexed. | In accordance with male contraception guidance for pemetrexed |
| Section 6.1: Study interventions administered | Updated "Table 2 Overview of study interventions administered" with pemetrexed details | To reflect the change of adding the combination arm of tusamitamab ravtansine with the SOC pembrolizumab, platinum-based chemotherapy and pemetrexed as Part C |
| Section 6.5: Concomitant therapy | Replaced "route of use" with "route of administration" | To clarify |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 6.6.1: Determination of recommended doses | Details on determination of recommended dose for Part C are added | To clarify the dose recommendation for Part C |
| | Dose modification and dose schedules for pemetrexed are added in Table 4 | To clarify the dose recommendation for Part C |
| Section 6.6.2: Individual dose modification | Added following text "If appropriate, and if in the opinion of the Investigator, the toxicity is related to one of the treatments, pembrolizumab, tusamitamab ravtansine, cisplatin/carboplatin or pemetrexed instead of the combination and more than 1 cycle delay is needed, this drug may be interrupted upon discussion with the sponsor, and the other drug(s) can be continued and this drug can only be resumed at following cycle after the toxicity recovers to Grade ≤1" | To clarify the dose modification for quadruplet combinations<br>To reflect the change of adding the combination arm of tusamitamab ravtansine with the SOC pembrolizumab, platinum-based chemotherapy and pemetrexed as Part C |
| | Dose reduction details of pemetrexed are added to Table 6 | To reflect the change of adding the combination arm of tusamitamab ravtansine with the SOC pembrolizumab, platinum-based chemotherapy and pemetrexed as Part C |
| Section 7.1.1: permanent discontinuation | Removed the following text "If study intervention is permanently discontinued, the participant may remain in the study for tumor assessment as described in Section 8.1. See the SoA for data to be collected at the time of discontinuation of study intervention". | To reflect the removal of tumor assessment |
| Section 8.1: Efficacy assessments | Removed the text related to RECIST 1.1 and ORR of Part A | To reflect the change of endpoints and sample size of Part A |
| Section 8.3.1: Time period and frequency for collecting AE and SAE information | Added following text "During prescreening period, only AEs/SAEs related to the fresh biopsy procedure (if applicable) and occurring within 1 month after the fresh biopsy will be recorded in the eCRF". | To clarify AEs/SAEs related to the fresh biopsy are recorded in eCRF |
| Section 8.5.1: Non-compartmental analysis | Removed the Table 7 "List of pharmacokinetic parameters and definitions" | To reflect the change in PK analysis (non-compartmental analysis will be replaced by population PK analysis) |
| Section 8.11: Use of Biological Samples and Data for Future Research | Section was updated as per new template text | To be consistent with the text in ICF |
| Section 9.4.1: General consideration | Removed Part A Statistical analysis details | To reflect the change of primary endpoint and sample size of Part A |
| Section 9.4.3.8: Pharmacokinetic variables | Removed the following text "The non-compartmental PK analysis will be described in the SAP and will be performed on the PK population". | To reflect the change in PK analysis (non-compartmental analysis will be replaced by population PK analysis) |
| Appendix 1: Section 10.1.4 Committees structure | Removed the following text "to safety run-in phase or Part B (as appropriate)" | To reflect the change in removal of Part 2 of Part A |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Appendix 2:<br>Section 10.2: CLINICAL LABORATORY TESTS | Replaced "tri-iodothyronine" with "Total tri-iodothyronine" and updated corresponding footnote in Table 7- Protocol-required laboratory assessments | To clarify that total T3 is preferred; if not available free T3 may be tested |
| Appendix 6 | Added recommended dose modification details of pemetrexed to Table 12 (hematological toxicity) and Table 13 (nonhematological toxicity) | To reflect the change of adding the combination arm of tusamitamab ravtansine with the SOC pembrolizumab, platinum-based chemotherapy and pemetrexed as Part C |
| Appendix 10 | Replaced the previous Appendix "MODIFIED RESPONSE EVALUATION CRITERIA IN SOLID TUMORS FOR IMMUNE BASED THERAPEUTICS" with "MASCC Corticosteroid Dosing Guidelines (2016 Guidelines)" | To reflect the removal of iRECIST |
| Throughout | Removed Part A and Part B and added "with or without pemetrexed" | Corresponding text modified to be suitable for Part A, Part B and Part C |

### Amended protocol 05 (04 July 2022)

This amended protocol 05 (Amendment 05) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

## OVERALL RATIONALE FOR THE AMENDMENT

The main purpose of this amendment is:

- To increase the number of participants treated at recommended Phase 2 dose (RP2D) in Part A (up to 20), Part B (up to 10 in each triplet) and Part C (up to 10 in each quadruplet), to better assess the safety data of each combination.
- To add moderate CEACAM5 expressors in Part A and in Part B in order to assess whether a doublet, or triplet combination might benefit to such patients.

**Protocol amendment summary of changes table**

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Whole document | Number and date of the amendment has been updated | To fit with the current amendment number and timeline. |
| Overall rationale for the amendment | This section is revised/ updated with the changed meant for amended protocol 05. Protocol amendment summary of changes (SOC) table also inserted with the necessary details. This is done in view of the objective of the amendment of assessing the safety data of each combination in a higher number of participants | To be compliant with the rationale of this new amendment. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.1. Synopsis: Rationale | Text was added to present the results from the NSCLC-Moderate CEACAM5 expressor cohort of Study TED13751 | To justify the inclusion of moderate CEACAM5 population. |
| | Text was added to define the moderate and high CEACAM5 expression | To justify the inclusion of moderate CEACAM5 population. |
| Section 1.1 Synopsis: Overall design, Part A; Part B; Part C; and Section 4.1 Overall Design, Part A; Part B; Part C | Number of participants has been updated in study overall design Part Am and the corresponding text is updated us follows. Total of up to 20 participants treated at the RP2D (leading to a total of up to 32 participants treated in Part A). Based on current enrollment, at least 9 DLT-evaluable participants will be included. | To assess the safety data in a higher number of participants. |
| | Number of participants has been updated in study overall design Part B, and the corresponding text is updated as follows: “The tolerability of each triplet platinum combination will be assessed in approximately 6 to 18 participants to determine the RP2D in each triplet platinum combination arm (carboplatin or cisplatin). It is planned to enroll additional participants to have a total of up to 10 participants treated at the RP2D in each triplet combination arm (leading to a total of approximately up to 44 participants treated in Part B)." | To assess the safety data in a higher number of participants. |
| Section 1.1 Synopsis: Number of Participants: Part A, Part B, and Part C. Statistical considerations: Part A and Part B, & 9.2. Statistical considerations: Sample size determination; Part A and Part B | Text was modified in order to reflect new number of participants to be enrolled in Part A, Part B, and Part C, according to new sample size calculation, after addition of moderate and high CEACAM5 expressors. | To align with new sample size calculation. |
| 1.1. Synopsis, overall design & 2.1 Study Rationale | Text was added to define high and moderate expression of CEACAM5 in immunohistochemistry analysis. | To have a concise definition of IHC analysis. |
| 1.3.2. PK/ATA Flowchart,<br>1.3.2.1 PK/ATA flow chart for Part A<br>1.3.2.2. PK/ATA flow chart for Part B &<br>1.3.2.2. PK/ATA flow chart for Part C. | Note regarding sampling time and stopping rules for PK and ATA was modified. | For clarity sampling procedures for site. |
| Section 1.2 Schema: Figure 2 | “DLTs at C1” has been removed from figure and DLT description has been removed from footnote. | To be consistent with Figure 3 and Figure 4 data. |
| Section 1.2 Schema: Figure 2; 3; 4 | The number of participants has been updated in all the figures. | To be compliant with the new higher number of participants in the whole study design. |
| Section 1.3.1 Study procedures flowchart | Changed PS to ECOG. | To clarify collection of ECOG status. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 1.3.1. Study procedures flowchart. | A new row was added to describe collection of age data.<br>The number of participants in Parts A, B & C have been updated.<br>Text has been added to clarify the recommended dose selection, escalation / de-escalation by DLT incidence. | To clarify the collection of age data.<br>To comply to new sample size determination.<br>To clarify recommended dose selection. |
| 1.2 Schema Figure 2 Graphical representation for Part A<br>Figure 3. Graphical representation for Part B &<br>Figure 4. Graphical representation for Part C | Text was added:<br>"up to 30 patients to be treated in RP2D".<br>"up to 10 patients to be treated in RP2D"<br>"up to 22 patients to be treated in RP2D"<br>"At least 2" is replaced by "At least 1"<br>"90 Days (±7 days) after last IMP" was added in the timeline | To reflect new study design and population. |
| Section 1.3.1 Study procedure flowchart | Footnote "m" was added | To clarify procedures under the new study design. |
| Section 2.1 Study rationale | Text was added to present the results from the NSCLC-Moderate CEACAM5 expressor cohort of Study TED13751.<br>Text was modified to describe patient population include moderate and high CEACAM5 expressors. | To justify the inclusion of moderate CEACAM5 population. |
| Section 2.3 Benefit/risk assessment | Text was added to refer to further risk/benefit data in the IB and Product Information documents. | To provide more information on risk/benefit assessment. |
| Section 4.1 Study design | Text has been added to describe collection of samples for CEACAM5 evaluation<br>Text was deleted: "'Participants with CEACAM5 moderate expression (≥1% and <50%) tumors will go through protocol screening procedures and be enrolled in Part C". | To clarify CEACAM5 evaluation.<br>To align with new study design that includes both moderate an high CEACAM5 expressos. |
| 5.1. Inclusion criteria | Text was added in inclusion criterion I04 to account for IHC intensity.<br>Text added: "≥2+ in intensity involving at least 1% of the tumor cell population in archival tumor sample" | To accommodate evaluation of CEACAM5 moderate and high status. |
| Section 6.6.1 Determination of recommended doses | "And other available information" has been added in selected paragraphs. | To provide further information on determining RP2D. |
| Section 1.1 Synopsis: Number of participants, 6.2.2 Preparation/ handling/storage/ accountability, 7.1.1 Heading<br>9.4.3.2 Adverse events, Section 10 Appendix 6 | The word "definite" was replaced by the word "permanent". | For better clarity of the term permanent discontinuation. |
| 8.6. Pharmacodynamics | Text has been added to specify sample collection related to IMP administration. | To clarify sampling procedures. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 10.1.5 Dissemination of clinical study data | Wed address with data sharing criteria was changed. | To update source for dissemination of clinical study data. |
| Section 10.3.1 Definition of AE | The two sentences:<br>"Symptomatic and/or"<br>- "Requiring either corrective treatment or consultation, and/or" have been removed in events meeting the AE definition. | To be consistent with AE reporting rules of oncology studies. |
| 10.8. Appendix 8. Table 14 | Table was updated with information on potent CYP3A Inhibitors. | To homogenize with other clinical trials from this program. |
| Section 10.6, Appendix 6, Table 9. | Change in recommendation in case of hepatic enzyme increase Grade 3. | To homogenize with other clinical trials from this program. |
| 10.13 Appending 13: Protocol amendment history | Text has been modified to include amendment 05. | To comply with Amendment protocol 05. |

In addition, other minor editorial changes (eg, grammatical, stylistic, and minor typographical corrections) were implemented throughout the protocol.

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