STATISTICAL ANALYSIS PLAN

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 non-squamous non-small-cell lung cancer (NSQ NSCLC)**
Protocol number:	**ACT16146**
Compound number (INN/Trademark):	**SAR408701** **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)**
Statistician:	[redacted]
Statistical project leader:	[redacted]
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TABLE OF CONTENTS

LIST OF TABLES

VERSION HISTORY

This amended statistical analysis plan (SAP) for Study ACT16146 is based on the amended protocol 04 dated 18-Aug-2021. This section summarizes the major changes to the statistical analysis features in the SAP. The first participant was randomized on 11-Mar-2021. The initial version of the SAP was approved before the first participant was randomized. This amended SAP is approved before the first step analysis is conducted.

The major changes in the SAP are related to changes following the protocol amendments:

- Protocol amendment 01: Adding a dose level of 170 mg/m² in safety run-in part of Part A for the tusamitamab ravtansine + pembrolizumab arm, and adding Part B, which consists of a safety run-in in 2 new triplet combination arms (tusamitamab ravtansine + pembrolizumab + cisplatin/carboplatin)
- Protocol amendment 03: Removing the pembrolizumab single-agent arm in Part A
- Protocol amendment 04: Adding Part C, which consists of a safety run-in in 2 new quadruplet combination arms (tusamitamab ravtansine + pembrolizumab + pemetrexed + cisplatin/carboplatin), removing Part 2 of Part A, moving ORR in Part A as secondary endpoint, and removing the other secondary efficacy endpoints (PFS, DOR, ORR per iRECIST)

Table 1 - Major changes in statistical analysis plan

SAP Version	Approval Date	Changes	Rationale
1.0	16-Sep-2020	Not Applicable	Original version
2.0	09-Nov-2021	Study design has been updated to add Part B and Part C, to remove pembrolizumab single-agent arm in Part A, and therefore to remove randomization in Part A, to remove Part 2 of Part A, to remove PD-L1 requirements in Part A, to add a dose level of 170 mg/m² in Part A, to update sample size of Part A.	To reflect last amended protocol 04.
		Study cut-offs have been updated	To reflect last amended protocol 04.
		Sample size of Part A has been updated.	To reflect last amended protocol 04.
		Objectives, endpoints and estimands have been updated to include Part B and Part C, to remove pembrolizumab single-agent arm in Part A, to move ORR in Part A as secondary endpoint, to remove other secondary efficacy endpoints (PFS, DOR, ORR per iRECIST).	To reflect last amended protocol 04.
		Statistical analyses have been added for Part B and Part C.	To reflect last amended protocol 04.
		Statistical analyses have been updated for Part A.	To reflect last amended protocol 04.
		Analysis populations have been updated to include Part B and Part C, and changes in Part A.	To reflect last amended protocol 04.

SAP Version	Approval Date	Changes	Rationale
		Analyses on COVID-19 have been added.	To assess the impact of the COVID-19 on the study.
		Analyses on slit lamp examination and on corneal events have been added.	To assess the occurrence and recurrence of corneal events, that are adverse events of interest.
		Tertiary/exploratory objective and endpoint of circulating CEA evaluation has been updated, and biomarkers analyses have been updated accordingly.	To reflect the additional collection of circulating CEA at pre-screening.
		Tertiary/exploratory objective and endpoint of cfDNA evaluation has been updated, and biomarkers analyses have been updated accordingly.	To reflect the additional collection of cfDNA at Cycle 5 Day 1.
		Analysis on time-to-next therapy has been removed.	Not appropriate with limited sample size and short follow-up duration in each study part.
		Pre-screening and screening categories for AE have been removed.	Pre-treatment category is sufficient for the analyses.
		Formula of corrected calcium was updated.	Correction of the formula.
		Details added in Section 4.9 on the different steps of analyses planned in the study.	To clarify the different steps of analyses planned in the study.

1 INTRODUCTION

1.1 STUDY DESIGN

This is a Phase 2, multicenter, multinational, open-label study which comprises 3 parts: Part A, Part B and Part C.

Part A is a single-group study part evaluating tusamitamab ravtansine in combination with pembrolizumab in Non-squamous Non-Small Cell Lung Cancer (NSQ NSCLC) participants with CEACAM5 high expression (CEACAM5 immunohistochemistry [IHC] intensity ≥2+ in ≥50% of tumor cells) tumors.

Part B is a 2 parallel-group study part evaluating tusamitamab ravtansine in combination with pembrolizumab and platinum-based chemotherapy (cisplatin or carboplatin) in NSQ NSCLC participants with CEACAM5 high expression tumors.

Part C is a 2 parallel-group study part evaluating tusamitamab ravtansine in combination with pembrolizumab, platinum-based chemotherapy (cisplatin or carboplatin), and pemetrexed in NSQ NSCLC participants with CEACAM5 high or moderate expression (CEACAM5 IHC intensity ≥2+ in ≥1% and <50% of tumor cells) tumors.

Screening phase will only be performed in pre-screened participants with NSQ NSCLC determined to be CEACAM5 moderate or high expressors by central IHC assessment. Participants with CEACAM5 high expression will be enrolled either in Part A, Part B, or Part C per investigator's choice. Participants with CEACAM5 moderate expression will be enrolled in Part C.

PART A:

In Part A, the tolerability and safety will be assessed and the recommended Phase 2 dose (RP2D) of tusamitamab ravtansine in combination with pembrolizumab will be determined.

Approximately 6 to 18 participants will be treated in order to determine the RP2D. It is planned to enroll additional participants to have a total of approximately 12 participants treated at the RP2D (leading to a total of approximately 6 to 24 participants treated in Part A).

PART B:

In Part B, the tolerability and safety of tusamitamab ravtansine in combination with pembrolizumab and platinum-based chemotherapy (cisplatin or carboplatin) will be assessed and the RP2Ds will be determined. Participants can be assigned to either cisplatin or carboplatin, per Investigator's choice.

Approximately 12 to 36 treated participants in the cisplatin and carboplatin combination arms in Part B (6 to 18 for each arm) are expected to be evaluable for tolerability and safety.

PART C:

In Part C, the tolerability and safety of tusamitamab ravtansine in combination with pembrolizumab, platinum-based chemotherapy (cisplatin or carboplatin), and pemetrexed will be assessed and the RP2Ds will be determined. Participants can be assigned to either cisplatin or carboplatin, per Investigator's choice.

Approximately 12 to 36 treated participants in the cisplatin and carboplatin combination arms in Part C (6 to 18 for each arm) are expected to be evaluable for tolerability and safety.

In Parts A, B and C, the cycle duration is 21 days for all combination arms. The DLT observation period is the first cycle. 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. The tolerability of each combination will be assessed in at least 6 participants.

The median expected duration of study per participant is estimated at 10 months (up to 1 month for screening, a median of 6 months for study intervention administration, a median of 1 month for end of treatment (EOT), and follow-up visit 90 days after the last administration of study intervention). Participants will continue to receive their assigned study intervention until confirmed disease progression, further anticancer therapies, unacceptable toxicity, or upon participant's request to stop the study intervention, or Investigator's decision, whichever occurs first.

1.2 OBJECTIVES AND ENDPOINTS

Table 2 - Objectives and endpoints

	Objectives	Endpoints
Primary		
	• 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 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
Secondary		
	• To assess the safety and tolerability of tusamitamab ravtansine in combination with pembrolizumab and tusamitamab ravtansine in combination with pembrolizumab and platinum-based chemotherapy with or without pemetrexed	• 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 tusamitamab ravtansine in combination with pembrolizumab and tusamitamab ravtansine in combination with pembrolizumab and platinum-based chemotherapy with or without 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 response evaluation criteria in solid tumors (RECIST) 1.1

	Objectives	Endpoints
	• 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 quadruplet (tusamitamab ravtansine + pembrolizumab + platinum-based chemotherapy + pemetrexed)	• Pharmacokinetic parameters of tusamitamab ravtansine, pembrolizumab, pemetrexed, cisplatin, and carboplatin
	• To assess the immunogenicity of tusamitamab ravtansine when given in combination with pembrolizumab and tusamitamab ravtansine in combination with pembrolizumab and platinum-based chemotherapy with or without pemetrexed	• Incidence of anti-therapeutic 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 pre-screening	• Circulating CEA at pre-screening, 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 at Cycle 5
	• To explore CEACAM5 expression on circulating tumoral cells (CTCs)	• CEACAM5 expression assessment on CTCs from patients with positive (moderate or high) CEACAM5 expression on tumor tissue

1.2.1 Estimands

Primary estimand defined for the primary endpoint is summarized in below Table 3. More details are provided in Section 4.

In this study, study interventions of interest are:

- tusamitamab ravtansine in combination with pembrolizumab in Part A,
- tusamitamab ravtansine in combination with pembrolizumab and platinum-based chemotherapy (cisplatin or carboplatin) in Part B,
- tusamitamab ravtansine in combination with pembrolizumab and platinum-based chemotherapy (cisplatin or carboplatin) and pemetrexed in Part C.

Table 3 - Summary of primary estimands for main endpoints

Endpoint Category (estimand)	Estimands			
	Endpoint	**Population**	**Intercurrent event(s) handling strategy**	**Population-level summary (Analysis and missing data handling)**
Primary objective: 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 in the NSQ NSCLC population				
Primary endpoint (primary estimand)	Study drug-related dose-limiting toxicity at Cycle 1, by dose level (if applicable).	DLT-evaluable population	Participants from the DLT-evaluable population will not experience any anticipated intercurrent events before experiencing a DLT at Cycle 1 or before completing the Cycle 1, whichever is earlier.	Incidence of study drug-related DLTs at Cycle 1, defined as the rate of participants with study-drug related DLTs at Cycle 1.

2 SAMPLE SIZE DETERMINATION

PART A:

Part A aims to establish the RP2D of tusamitamab ravtansine in combination with pembrolizumab according to DLTs observed.

The actual sample size is expected to vary depending on DLTs observed. It is anticipated that 6 to 24 DLT-evaluable participants (as defined in Section 3) will be treated with tusamitamab ravtansine + pembrolizumab: up to 12 DLT-evaluable participants at DL other than the RP2D, and 12 DLT-evaluable participants at the RP2D.

Assuming a pre-screening failure rate of 80% and a study screening failure rate of 20%, approximately 38 to 150 participants will be pre-screened to achieve 6 up to 24 DLT-evaluable participants.

PART B:

Part B of the study aims to establish the RP2Ds of tusamitamab ravtansine in combination with pembrolizumab and platinum-based chemotherapy (cisplatin or carboplatin) according to DLTs observed.

The actual sample size is expected to vary depending on DLTs observed. It is anticipated that in each triplet combination arm, 6 to 18 DLT-evaluable participants (as defined in Section 3) will be treated with tusamitamab ravtansine + pembrolizumab + cisplatin or carboplatin: up to 12 DLT-evaluable participants in each triplet combination arm at DL other than the RP2D, and 6 DLT-evaluable participants at the RP2D.

Assuming a pre-screening failure rate of 80% and a study screening failure rate of 20%, approximately 75 to 225 participants will be pre-screened to achieve 12 to 36 DLT-evaluable participants in Part B (6 to 18 DLT-evaluable participants in each triplet combination arm).

PART C:

Part C of the study aims to establish the RP2Ds of tusamitamab ravtansine in combination with pembrolizumab, pemetrexed and platinum-based chemotherapy (cisplatin or carboplatin) according to DLTs observed.

The actual sample size is expected to vary depending on DLTs observed. It is anticipated that in each quadruplet combination arm, 6 to 18 DLT-evaluable participants (as defined in Section 3) will be treated with tusamitamab ravtansine + pembrolizumab + pemetrexed + cisplatin or carboplatin: up to 12 DLT-evaluable participants in each quadruplet combination arm at DL other than the RP2D, and 6 DLT-evaluable participants at the RP2D.

Assuming a pre-screening failure rate of 45% and a study screening failure rate of 20%, approximately 28 to 82 participants will be pre-screened to achieve 12 to 36 DLT-evaluable participants in Part C (6 to 18 DLT-evaluable participants in each quadruplet combination arm).

3 ANALYSIS POPULATIONS

The following populations for analyses are defined:

Table 4 - Populations for analyses

Population	Description
Pre-screened	All participants who signed the pre-screening informed consent for CEACAM5 assessment of their biopsy.
Screened	All participants who signed screening informed consent for study participation.
Enrolled	Participants from screened population who have been allocated to intervention regardless of whether the intervention was received or not.
All-treated	All participants assigned to study intervention and who have actually received at least one 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 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 participants from the all-treated population with at least 1 post-baseline PK concentration with adequate documentation of dosing and sampling dates and times.
ATA	All participants from the all-treated population with at least 1 post-baseline ATA result (negative, positive, or inconclusive).
Population without trial impact (disruption) due to COVID-19	All treated participants: • without any critical or major deviation related to COVID-19, • and who did not permanently discontinue study intervention due to COVID-19, • and who did not permanently discontinue study due to COVID-19.

ATA = anti-therapeutic antibodies; CEACAM5 = carcinoembryonic antigen-related cell adhesion molecule 5; DLT = dose-limiting toxicity; IMP = investigational medicinal product; PK = pharmacokinetic.

In practice, a participant will be included in the enrolled population if the question “Will the subject continue in the treatment phase?” has been answered as “Yes” in the “Completion of screening phase” e-CRF page. It includes any participants randomized in Part A before protocol amendment 03.

In practice, a participant will be included in the DLT-evaluable population if “Dose Limiting Toxicities” e-CRF page has been filled in at the end of Cycle 1. This includes participants followed up to the end of the DLT observation period or participants having experienced a DLT before the end of the DLT observation period and validated by the Study Committee. Participants with an overdose (defined as a dose received at least 30% above the intended dose) of any IMP of the combination at Cycle 1 will be excluded from the DLT-evaluable population.

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

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

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

4 STATISTICAL ANALYSES

4.1 GENERAL CONSIDERATIONS

Efficacy endpoint based on radiological assessments of tumor burden (confirmed objective response) will be derived using the local radiologist's/Investigator's assessment.

In general, continuous data will be summarized using the number of observations available, mean, standard deviation (SD), median, Q1, Q3, minimum, and maximum. Categorical and ordinal data will be summarized using the count and percentage of participants.

The baseline value is defined as the last available value before the first dose of investigational medicinal product (IMP).

Unless otherwise specified, analyses will be performed by intervention arm (and overall, for baseline, demographics characteristics and safety) on each study part separately.

The study cut-off for the primary safety endpoints analysis (DLT) will be at the end of the first cycle of the last participant treated to determine the RP2D in Part A, Part B or Part C.

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

The analysis cut-off date is defined as the date of the database extraction that will be performed for the analysis.

Observation period

The observation period will be divided into 4 segments:

- The **pre-treatment period** is defined as the period up to first IMP administration.
  - The **pre-screening period** is defined as the period from the pre-screening informed consent to the day before the screening informed consent.
  - The **screening period** is defined as the period from the screening informed consent up to the first IMP administration.
- The **on-treatment period** (ie, **treatment-emergent period**) is defined as the period from the first IMP administration to the last IMP administration +30 days.
- The **post-treatment period** is defined as the period from the end of the on-treatment period.

4.2 PARTICIPANT DISPOSITIONS

The number (%) of participants included in each of the analysis populations listed in Table 4 will be summarized. Reasons for exclusion from the population without trial impact (disruption) due to COVID-19 will be summarized.

Pre-screen failures are defined as participants who consent to participate in the pre-screening phase of the study but are not subsequently screened. The number (%) of pre-screen failures and reasons for pre-screen failures will be provided in the pre-screened population.

Screen failures are defined as participants who consent to participate in the study but are not subsequently enrolled. The number (%) of screen failures and reasons for screen failures will be provided in the screened population.

Regarding study intervention discontinuation, the following definitions will be used:

- Permanent **partial** intervention discontinuation is defined as the discontinuation of at least one of the study drugs but at least one is continued.
- Permanent **full** intervention discontinuation is defined as the discontinuation of all the study drugs.

The number (%) of participants in the following categories will be provided:

- Enrolled participants
- Enrolled but not treated participants
- Enrolled and treated participants
- Participants still on study intervention
- Participants who discontinued the study intervention and main reason for permanent full intervention discontinuation
- Participants who discontinued the study intervention and main reason for permanent partial discontinuation of tusamitamab ravtansine
- Participants who discontinued the study intervention and main reason for permanent partial discontinuation of pembrolizumab
- Participants who discontinued the study intervention and main reason for permanent partial discontinuation of cisplatin
- Participants who discontinued the study intervention and main reason for permanent partial discontinuation of carboplatin
- Participants who discontinued the study intervention and main reason for permanent partial discontinuation of pemetrexed
- Participants who discontinued the study and main reason for study discontinuation

Reasons for permanent full/partial study intervention discontinuation and study discontinuation such as “adverse event” and “other reasons” will be split as related or not related to COVID-19 (if applicable).

The number (%) of treated and not enrolled participants will also be summarized.

In addition, the number (%) of participants pre-screened, pre-screen failed, screened, screen failed, enrolled, enrolled and treated, with permanent full study intervention discontinuation and with study discontinuation, will be provided by country and site.

For all categories of participants (except for the pre-screened, screened and non-enrolled categories) percentages will be calculated using the number of participants in the all-treated population as the denominator.

Protocol deviations

Critical and major protocol deviations (automatic or manual) will be summarized in the all-treated population as well as displayed separately as related or not related to COVID-19 (if applicable).

4.3 PRIMARY ENDPOINT ANALYSIS

4.3.1 Definition of endpoint

The primary endpoint is study-drug related DLT at Cycle 1 (from C1D1 to C1D21). List of DLTs to be considered in the study is defined in the protocol (see Section 6.6.1 of the study protocol). For analysis purposes, DLTs will be identified based on the AEs reported on the e-CRF DLT page during the DLT observation period.

4.3.2 Main analytical approach

The primary safety analysis is based on the primary estimand introduced in Section 1.2.1. It is defined according to the following attributes:

- The endpoint is study-drug related DLT during the DLT observation period, ie, Cycle 1, from Cycle 1 Day 1 to Cycle 1 Day 21.
- The treatment condition of interest is:
  - For Part A: tusamitamab ravtansine in combination with pembrolizumab, by dose level (if applicable).
  - For Part B: tusamitamab ravtansine in combination with pembrolizumab and platinum-based chemotherapy (cisplatin or carboplatin), by dose level (if applicable).
  - For Part C: tusamitamab ravtansine in combination with pembrolizumab, pemetrexed and platinum-based chemotherapy (cisplatin or carboplatin), by dose level (if applicable).
- The analysis population is the DLT-evaluable population (defined in Section 3).

- No intercurrent events handling strategy is defined due to the definition of the analysis population. Indeed, participants from the DLT-evaluable population will not experience any anticipated intercurrent events (study intervention discontinuation, start of an anticancer therapy and death) before experiencing a DLT at Cycle 1 or before completing the Cycle 1, whichever is earlier.
- Population-level summary will include the incidence of DLTs at Cycle 1, defined as number and percentage of participants experiencing at least one study-drug related DLT. There will be no missing data in the analysis population.

4.3.3 Sensitivity analysis

No sensitivity analysis is planned in this study.

4.3.4 Supplementary analyses

No supplementary analysis is planned in this study.

4.3.5 Subgroup analyses

No subgroup analysis is planned in this study.

4.4 SECONDARY ENDPOINT ANALYSIS

The secondary endpoint detailed in this section is the confirmed objective response. Other secondary endpoints analyses are defined in Section 4.7 (AE, SAE, laboratory abnormalities) and Section 4.8 (PK, immunogenicity).

4.4.1 Key/Confirmatory secondary endpoint

No key/confirmatory secondary endpoint.

4.4.2 Supportive secondary endpoint

4.4.2.1 Definition of endpoint

The secondary efficacy endpoint is confirmed objective response determined according to RECIST 1.1. A confirmed objective response is defined as a confirmed CR or PR as best overall response (BOR).

The BOR will be derived according to RECIST 1.1 definitions (1, 2) based on the investigator's assessment. The BOR is the best overall response observed from the date of the first administration of IMP until documented disease progression, death, start of an anticancer therapy, or analysis cut-off date, whichever occurs first.

4.4.2.2 Main analytical approach

The secondary efficacy analysis is based on an estimand defined according to the following attributes:

- The endpoint is confirmed objective response (confirmed CR or PR as BOR) as per RECIST 1.1.
- The treatment condition of interest is:
  - For Part A: tusamitamab ravtansine in combination with pembrolizumab, by dose level (if applicable).
  - For Part B: tusamitamab ravtansine in combination with pembrolizumab and platinum-based chemotherapy (cisplatin or carboplatin), by dose level (if applicable).
  - For Part C: tusamitamab ravtansine in combination with pembrolizumab, pemetrexed and platinum-based chemotherapy (cisplatin or carboplatin), by dose level (if applicable).
- The analysis population is the all-treated population (defined in Section 3).
- Intercurrent events:
  - The study intervention discontinuation intercurrent event will be handled with the treatment policy strategy. Confirmed objective response will be assessed based on tumor assessments regardless of study intervention discontinuation.
  - The further anticancer therapy (including further systemic anticancer therapies) intercurrent event will be handled with the "while not initiating further anticancer therapy" strategy. Confirmed objective response will be assessed based on tumor assessments up to the time of initiation of further anticancer therapy.
- The population-level summary will include the ORR, by combination arm, defined as the rate of participants with confirmed objective response and two-sided 95% confidence intervals using the Clopper-Pearson method. In addition, ORR may be summarized combining both triplet combination arms, and both quadruplet combination arms. In addition, the number (%) of participants within each BOR category, including not evaluable as per RECIST 1.1 and reason for being not evaluable will be provided.

  In the absence of confirmed objective response before the analysis cut-off date (taking into account the intercurrent event handling strategies), participants will be considered as non-responders, whatever the reason (including participants with non-evaluable BOR).

4.5 TERTIARY/EXPLORATORY ENDPOINTS ANALYSIS

Other tertiary/exploratory endpoints (eg, biomarkers) are defined in Section 4.8.

4.6 MULTIPLICITY ISSUES

No multiplicity issues.

4.7 OTHER SAFETY ANALYSES

All safety analyses will be performed on the all-treated population as defined in Section 3, by dose level (if applicable) and overall, unless otherwise specified, using the following common rules:

- The analysis of the safety variables will be essentially descriptive, and no testing is planned.
- Safety data in participants who do not belong to the all-treated population (eg, treated but not enrolled) will be provided.

4.7.1 Extent of exposure

4.7.1.1 Overall exposure

The dose information will be assessed by the following variables:

- Overall number of cycles started, defined by the number of cycles in which at least one dose of any study intervention is administered.
- Duration of IMP exposure (in weeks), defined as (last day of exposure - first day of exposure + 1)/7.
  - The first day of exposure is defined as the first administration date with non-zero dose for at least one of the IMP (tusamitamab ravtansine, pembrolizumab, pemetrexed, cisplatin, or carboplatin).
  - The last day of exposure is the day before the theoretical date of the next administration (after the last administration), defined as last administration date of at least one IMP + 21 days - 1 (for tusamitamab ravtansine, pembrolizumab, pemetrexed, cisplatin or carboplatin).

The total number of cycles started, and the number of cycles started by participants will be summarized as a quantitative variable and by category (number (%) of participants receiving at least 1 cycle, at least 2 cycles, etc.). The duration of overall exposure will be summarized quantitatively.

The following variable will be computed to describe overall dose modification (cycle delay):

- Cycle delay: A cycle is deemed as delayed if the start date of the current cycle - 21 days - start date of the previous cycle is >3 days. Cycle delay is not defined for the first cycle.

Cycle delay will be analyzed at the participant (with number of participants used as denominator) and cycle (with number of cycles used as denominator) levels, as follows:

- Number (%) of participants with a least 1 cycle delayed
  - Number (%) of participants with a cycle delayed between 4 and 7 days (using maximum delay across all cycles)

  - Number (%) of participants with a cycle delayed >7 days (using maximum delay across all cycles)
- Number (%) of cycles delayed
  - Number (%) of cycles delayed between 4 and 7 days
  - Number (%) of cycles delayed >7 days

In addition, summaries will be provided by trial impact (disruption) due to COVID-19 (if applicable).

4.7.1.2 Tusamitamab ravtansine exposure

The dose information will be assessed by the following:

- Total number of cycles started
- Number of cycles started per participant
- Duration of tusamitamab ravtansine exposure (in weeks) is defined by date of last administration of tusamitamab ravtansine + 21 days - date of first administration of tusamitamab ravtansine/7
- Actual dose (in mg/m²). In case of dose interruption, actual dose will be the sum of the actual doses administered before and after the dose interruption.
- Cumulative dose (in mg/m²): the cumulative dose is the sum of all actual doses of tusamitamab ravtansine, given from first to last administration
- Actual dose intensity (ADI in mg/m²/week), defined as the cumulative dose divided by the duration of tusamitamab ravtansine exposure (in weeks)
- Planned dose intensity (PDI in mg/m²/week): corresponds to the planned dose multiplied by the theoretical total number of doses started and divided by the theoretical cycle duration expressed in weeks (ie, 3 weeks per cycle started)
- Relative dose intensity (RDI, in %): $100 \times \frac{\text{ADI (mg/m}^2\text{/week)}}{\text{PDI (mg/m}^2\text{/week)}}$

The total number of cycles started, and the number of cycles started by participant will be summarized as a quantitative variable and by category (number [%] of participants receiving at least 1 cycle, at least 2 cycles, etc). Duration of tusamitamab ravtansine exposure, cumulative dose, ADI and RDI will be summarized quantitatively.

The following variables will be derived to describe dose modifications and dose interruptions:

- Dose reduction: The first administration will not be counted as a dose reduction. For the second and subsequent tusamitamab ravtansine administrations, dose reduction will be determined using the dose level intervals provided in Table 5, by comparing the current dose level to the previous dose level. If the current dose level is below the dose level interval of the previous dose administration, then the current dose level is considered reduced.

Table 5 - Tusamitamab ravtansine dose reduction criteria

Actual dose level	Dose level interval
Dose level +1 (170 mg/m²)	>160 mg/m²
Starting dose (150 mg/m²)	>135 mg/m² and ≤160 mg/m²
Dose level -1 (120 mg/m²)	>110 mg/m² and ≤135 mg/m²
Dose level -2 (100 mg/m²)	>90 mg/m² and ≤110 mg/m²
Dose level -3 (80 mg/m²)	>70 mg/m² and ≤90 mg/m²
Low dose	>0 mg/m² and ≤70 mg/m²

- Dose delay: A dose will be considered as delayed if the tusamitamab ravtansine administration date of the current cycle – 21 days – tusamitamab ravtansine administration date of the previous cycle is >3 days. Dose delay is not defined for the first cycle, and for subsequent cycles in case tusamitamab ravtansine is not administered at previous cycle.
- Dose omission is defined as a dose not administered at the scheduled visit but administered afterwards.
- Dose interruption: A dose will be considered to be interrupted if the tusamitamab ravtansine administration is stopped during an infusion regardless of whether it is restarted or not.

Dose modifications will be analyzed by participant and cycle as follows:

- **Participant** (number of participants treated will be used as denominator)
  - Number (%) of participants with at least 1 dose modification
    - Number (%) of participants with at least 1 dose delayed
    - Number (%) of participants with at least 1 dose reduction
    - Number (%) of participants with at least 1 dose omission
  - Number (%) of participants with a least 1 dose interruption
- **Cycle** (number of cycles started will be used as denominator)
  - Number (%) of cycles with at least 1 dose modification
    - Number (%) of participants with at least 1 dose delayed
    - Number (%) of cycles with at least 1 dose reduction
    - Number (%) of cycles with at least 1 dose omission
  - Number (%) of cycles with at least 1 dose interruption

4.7.1.3 Pembrolizumab exposure

The dose information will be assessed by the following:

- Total number of cycles started

- Number of cycles started per participant
- Duration of pembrolizumab exposure (in weeks), defined by date of last administration of pembrolizumab + 21 days - date of first administration of pembrolizumab/7.
- Actual dose (in mg). In case of dose interruption, actual dose will be the sum of the actual doses administered before and after the dose interruption.
- Cumulative dose (in mg): the cumulative dose is the sum of all actual doses of pembrolizumab, given from first to last administration
- Actual dose intensity (ADI in mg/week): defined as the cumulative dose divided by the duration of pembrolizumab exposure (in weeks)
- Planned dose intensity (PDI in mg/week): corresponds to the planned dose multiplied by the theoretical total number of doses started and divided by the theoretical cycle duration expressed in weeks (ie, 3 weeks per cycle started)
- Relative dose intensity (RDI, in %): $100 \times \frac{\text{ADI (mg/week)}}{\text{PDI (mg/week)}}$

The total number of cycles started, and the number of cycles started by participant will be summarized as a quantitative variable and by category (number [%] of participants receiving at least 1 cycle, at least 2 cycles, etc). Duration of pembrolizumab exposure, cumulative dose, ADI and RDI will be summarized quantitatively.

The following variable will be derived to describe dose modifications and dose interruptions:

- Dose delay: A dose will be considered as delayed if the pembrolizumab administration date of the current cycle – 21 days – pembrolizumab administration date of the previous cycle is >3 days. Dose delay is not defined for the first cycle, and for subsequent cycles in case pembrolizumab is not administered at previous cycle.
- Dose interruption: A dose will be considered to be interrupted if the pembrolizumab administration is stopped during an infusion regardless of whether it is restarted or not.
- Dose omission is defined as a dose not administered at the scheduled visit but administered afterwards.

Dose modifications will be analyzed by participant and cycle as follows:

- **Participant** (number of participants treated will be used as denominator)
  - Number (%) of participants with at least 1 dose modification
    - Number (%) of participants with at least 1 dose delayed
    - Number (%) of participants with at least 1 dose omission
  - Number (%) of participants with a least 1 dose interruption

- **Cycle** (number of cycles started will be used as denominator)
  - Number (%) of cycles with at least 1 dose modification
    - Number (%) of cycles with at least 1 dose delayed
    - Number (%) of cycles with at least 1 dose omission
  - Number (%) of cycles with at least 1 dose interruption

4.7.1.4 Cisplatin exposure (Part B and Part C)

The dose information will be assessed by the following:

- Total number of cycles started
- Number of cycles started per participant
- Duration of cisplatin exposure (in weeks) is defined by date of last administration of cisplatin + 21 days - date of first administration of cisplatin/7
- Actual dose (in mg/m²). In case of dose interruption, actual dose will be the sum of the actual doses administered before and after the dose interruption.
- Cumulative dose (in mg/m²): the cumulative dose is the sum of all actual doses of cisplatin, given from first to last administration
- Actual dose intensity (ADI in mg/m²/week), defined as the cumulative dose divided by the duration of cisplatin exposure (in weeks)
- Planned dose intensity (PDI in mg/m²/week): corresponds to the planned dose multiplied by the theoretical total number of doses started and divided by the theoretical cycle duration expressed in weeks (ie, 3 weeks per cycle started)
- Relative dose intensity (RDI, in %): $100 \times \frac{\text{ADI (mg/m}^2\text{/week)}}{\text{PDI (mg/m}^2\text{/week)}}$

The total number of cycles started, and the number of cycles started by participant will be summarized as a quantitative variable and by category (number [%] of participants receiving at least 1 cycle, at least 2 cycles, etc). Duration of cisplatin exposure, cumulative dose, ADI and RDI will be summarized quantitatively.

The following variables will be derived to describe dose modifications and dose interruptions:

- Dose reduction: The first administration will not be counted as a dose reduction. For the second and subsequent cisplatin administrations, dose reduction will be determined using the dose level intervals provided in Table 6, by comparing the current dose level to the previous dose level. If the current dose level is below the dose level interval of the previous dose administration, then the current dose level is considered reduced.

Table 6 - Cisplatin dose reduction criteria

Actual dose level	Dose level interval
Starting dose (75 mg/m²)	>65.5 mg/m²
Dose level -1 (56 mg/m²)	>47 mg/m² and ≤65.5 mg/m²
Dose level -2 (38 mg/m²)	>29 mg/m² and ≤47 mg/m²
Low dose	>0 mg/m² and ≤29 mg/m²

- Dose delay: A dose will be considered as delayed if the cisplatin administration date of the current cycle – 21 days – cisplatin administration date of the previous cycle is >3 days. Dose delay is not defined for the first cycle, and for subsequent cycles in case cisplatin is not administered at previous cycle.
- Dose omission is defined as a dose not administered at the scheduled visit but administered afterwards.
- Dose interruption: A dose will be considered to be interrupted if the cisplatin administration is stopped during an infusion regardless of whether it is restarted or not.

Dose modifications will be analyzed by participant and cycle as follows:

- **Participant** (number of participants treated will be used as denominator)
  - Number (%) of participants with at least 1 dose modification
    - Number (%) of participants with at least 1 dose delayed
    - Number (%) of participants with at least 1 dose reduction
    - Number (%) of participants with at least 1 dose omission
  - Number (%) of participants with a least 1 dose interruption
- **Cycle** (number of cycles started will be used as denominator)
  - Number (%) of cycles with at least 1 dose modification
    - Number (%) of participants with at least 1 dose delayed
    - Number (%) of cycles with at least 1 dose reduction
    - Number (%) of cycles with at least 1 dose omission
  - Number (%) of cycles with at least 1 dose interruption

4.7.1.5 Carboplatin exposure (Part B and Part C)

The dose information will be assessed by the following:

- Total number of cycles started
- Number of cycles started per participant
- Duration of carboplatin exposure (in weeks) is defined by date of last administration of carboplatin + 21 days - date of first administration of carboplatin/7

- Actual dose (in mg/mL/min). In case of dose interruption, actual dose will be the sum of the actual doses administered before and after the dose interruption.
- Cumulative dose (in mg/mL/min): the cumulative dose is the sum of all actual doses of carboplatin, given from first to last administration
- Actual dose intensity (ADI in mg/mL/min/week), defined as the cumulative dose divided by the duration of carboplatin exposure (in weeks)
- Planned dose intensity (PDI in mg/mL/min/week): corresponds to the planned dose multiplied by the theoretical total number of doses started and divided by the theoretical cycle duration expressed in weeks (ie, 3 weeks per cycle started)
- Relative dose intensity (RDI, in %): $100 \times \frac{\text{ADI (mg/mL/min/week)}}{\text{PDI (mg/mL/min/week)}}$

The total number of cycles started, and the number of cycles started by participant will be summarized as a quantitative variable and by category (number [%] of participants receiving at least 1 cycle, at least 2 cycles, etc). Duration of carboplatin exposure, cumulative dose, ADI and RDI will be summarized quantitatively.

The following variables will be derived to describe dose modifications and dose interruptions:

- Dose reduction: The first administration will not be counted as a dose reduction. For the second and subsequent carboplatin administrations, dose reduction will be determined using the dose level intervals provided in Table 7, by comparing the current dose level to the previous dose level. If the current dose level is below the dose level interval of the previous dose administration, then the current dose level is considered reduced.

Table 7 - Carboplatin dose reduction criteria

Actual dose level	Dose level interval
Starting dose (5 mg/mL/min)	>4.4 mg/mL/min
Dose level -1 (3.75 mg/mL/min)	>3.1 mg/mL/min and ≤4.4 mg/mL/min
Dose level -2 (2.5 mg/mL/min)	>1.9 mg/mL/min and ≤3.1 mg/mL/min
Low dose	>0 mg/mL/min and ≤1.9 mg/mL/min

- Dose delay: A dose will be considered as delayed if the carboplatin administration date of the current cycle – 21 days – carboplatin administration date of the previous cycle is >3 days. Dose delay is not defined for the first cycle, and for subsequent cycles in case carboplatin is not administered at previous cycle.
- Dose omission is defined as a dose not administered at the scheduled visit but administered afterwards.
- Dose interruption: A dose will be considered to be interrupted if the carboplatin administration is stopped during an infusion regardless of whether it is restarted or not.

Dose modifications will be analyzed by participant and cycle as follows:

- **Participant** (number of participants treated will be used as denominator)
  - Number (%) of participants with at least 1 dose modification
    - Number (%) of participants with at least 1 dose delayed
    - Number (%) of participants with at least 1 dose reduction
    - Number (%) of participants with at least 1 dose omission
  - Number (%) of participants with a least 1 dose interruption
- **Cycle** (number of cycles started will be used as denominator)
  - Number (%) of cycles with at least 1 dose modification
    - Number (%) of participants with at least 1 dose delayed
    - Number (%) of cycles with at least 1 dose reduction
    - Number (%) of cycles with at least 1 dose omission
  - Number (%) of cycles with at least 1 dose interruption

4.7.1.6 Pemetrexed exposure (Part C)

The dose information will be assessed by the following:

- Total number of cycles started
- Number of cycles started per participant
- Duration of pemetrexed exposure (in weeks) is defined by date of last administration of pemetrexed + 21 days - date of first administration of pemetrexed/7
- Actual dose (in mg/m²). In case of dose interruption, actual dose will be the sum of the actual doses administered before and after the dose interruption.
- Cumulative dose (in mg/m²): the cumulative dose is the sum of all actual doses of pemetrexed, given from first to last administration
- Actual dose intensity (ADI in mg/m²/week), defined as the cumulative dose divided by the duration of pemetrexed exposure (in weeks)
- Planned dose intensity (PDI in mg/m²/week): corresponds to the planned dose multiplied by the theoretical total number of doses started and divided by the theoretical cycle duration expressed in weeks (ie, 3 weeks per cycle started)
- Relative dose intensity (RDI, in %): $100 \times \frac{\text{ADI (mg/m}^2\text{/week)}}{\text{PDI (mg/m}^2\text{/week)}}$

The total number of cycles started, and the number of cycles started by participant will be summarized as a quantitative variable and by category (number [%] of participants receiving at least 1 cycle, at least 2 cycles, etc). Duration of pemetrexed exposure, cumulative dose, ADI and RDI will be summarized quantitatively.

The following variables will be derived to describe dose modifications and dose interruptions:

- Dose reduction: The first administration will not be counted as a dose reduction. For the second and subsequent pemetrexed administrations, dose reduction will be determined using the dose level intervals provided in Table 8, by comparing the current dose level to the previous dose level. If the current dose level is below the dose level interval of the previous dose administration, then the current dose level is considered reduced.

Table 8 - Pemetrexed dose reduction criteria

Actual dose level	Dose level interval
Starting dose (500 mg/m²)	>437.5 mg/m²
Dose level -1 (375 mg/m²)	>312.5 mg/m² and ≤437.5 mg/m²
Dose level -2 (250 mg/m²)	>187.5 mg/m² and ≤312.5 mg/m²
Low dose	>0 mg/m² and ≤187.5 mg/m²

- Dose delay: A dose will be considered as delayed if the pemetrexed administration date of the current cycle – 21 days – pemetrexed administration date of the previous cycle is >3 days. Dose delay is not defined for the first cycle, and for subsequent cycles in case pemetrexed is not administered at previous cycle.
- Dose omission is defined as a dose not administered at the scheduled visit but administered afterwards.
- Dose interruption: A dose will be considered to be interrupted if the pemetrexed administration is stopped during an infusion regardless of whether it is restarted or not.

Dose modifications will be analyzed by participant and cycle as follows:

- **Participant** (number of participants treated will be used as denominator)
  - Number (%) of participants with at least 1 dose modification
    - Number (%) of participants with at least 1 dose delayed
    - Number (%) of participants with at least 1 dose reduction
    - Number (%) of participants with at least 1 dose omission
  - Number (%) of participants with a least 1 dose interruption
- **Cycle** (number of cycles started will be used as denominator)
  - Number (%) of cycles with at least 1 dose modification
    - Number (%) of participants with at least 1 dose delayed
    - Number (%) of cycles with at least 1 dose reduction
    - Number (%) of cycles with at least 1 dose omission
  - Number (%) of cycles with at least 1 dose interruption

4.7.2 Adverse events

General common rules for adverse events

All AEs will be graded according to National cancer institute common terminology for adverse events (NCI-CTCAE Version 5.0) and coded to a lower-level term (LLT), preferred term (PT), high-level term (HLT), high-level group term (HLGT), and associated primary system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA) version currently in effect at Sanofi at the time of database lock.

The AEs will be analyzed in the following 3 categories:

- Pre-treatment AEs: AEs that developed, worsened or became serious during the pre-treatment period.
- Treatment-emergent adverse events (TEAEs): AEs that developed, worsened or became serious during the treatment-emergent period.
- Post-treatment AEs: AEs that developed, worsened or became serious during the post-treatment period.

Similarly, the deaths will be analyzed in the pre-treatment, treatment-emergent and post-treatment periods.

The primary AE analyses will be on TEAEs. Pre-treatment AEs and post-treatment AEs will be described separately.

An AE with incomplete or missing date/time of onset (occurrence, worsening, or becoming serious) will be classified as a TEAE unless there is definitive information to determine it is a pre-treatment or a post-treatment AE.

If the assessment of the relationship to IMP is missing for an AE, this AE will be assumed as related to IMP if IMP is actually received by the participant, and as not related otherwise. Missing grade will be left as missing.

Multiple occurrences of the same event in the same participant will be counted only once in the tables within a treatment phase, using the maximum (worst) grade by treatment phase. Summaries will be provided for all grades combined and for grade ≥3 (including Grade 5). Missing grades, if any, will be included in the “all grades” category.

The AE tables will be sorted as indicated in Table 9.

Table 9 - Sorting of AE tables

AE presentation	Sorting rules
SOC, HLGT, HLT and PT	By the internationally agreed SOC order and by alphabetic order of HLGTs, HLTs and PTs.
SOC and PT	By the internationally agreed SOC order and decreasing frequency of PTs[a, b]
SMQ/CMQ and PT	By decreasing frequency of SMQs/CMQs and PTs[a]
PT	By decreasing frequency of PTs[a]

a Sorting will be based on the experimental intervention arm at the highest dose level.
b The table of all TEAEs presented by primary SOC and PT will define the presentation order for all other tables (eg, treatment-emergent SAE) presented by primary SOC and PT, unless otherwise specified.

Analysis of all adverse events

The overview of TEAE with the details below will be generated:

- Any TEAE
- Any grade ≥3 TEAE
- Grade 5 TEAE (any TEAE with a fatal outcome during the treatment-emergent period)
- Any treatment-emergent SAE
- Any treatment emergent AESI
- Any TEAE leading to permanent full study intervention discontinuation
- Any TEAE leading to permanent partial discontinuation of tusamitamab ravtansine
- Any TEAE leading to permanent partial discontinuation of pembrolizumab
- Any TEAE leading to permanent partial discontinuation of cisplatin
- Any TEAE leading to permanent partial discontinuation of carboplatin
- Any TEAE leading to permanent partial discontinuation of pemetrexed
- Any TEAE related to IMP
- Any grade ≥3 TEAE related to IMP
- Any treatment-emergent SAE related to IMP
- Any treatment-emergent corneal event (CMQ “Corneal events compound level”)
- Any ocular/visual symptoms TEAE (CMQ “Eye disorders exclude corneal disorders”),
- Any treatment-emergent peripheral neuropathy event TEAE (SMQ “Peripheral neuropathy” (Narrow and Broad))

The AE summaries of Table 10 will be generated with number (%) of participants experiencing at least one event. The analyses will be performed for all grades combined and for grades ≥3. The all TEAE summary by primary SOC and PT (and other safety summaries (eg, SAEs, deaths), if deemed needed after TEAE evaluation) will be performed by trial impact (disruption) due to COVID-19.

Table 10 - Analyses of adverse events

Type of AE	MedDRA levels
All TEAE	Primary SOC, HLGT, HLT and PT
	Primary SOC and PT
	PT
TEAE related to IMP as per Investigator's judgment	Primary SOC and PT
TEAE related to tusamitamab ravtansine as per Investigator's judgment	Primary SOC and PT
TEAE related to pembrolizumab as per Investigator's judgment	Primary SOC and PT
TEAE related to cisplatin as per Investigator's judgment	Primary SOC and PT
TEAE related to carboplatin as per Investigator's judgment	Primary SOC and PT
TEAE related to pemetrexed as per Investigator's judgment	Primary SOC and PT
Treatment emergent SAE	Primary SOC, HLGT, HLT and PT
	Primary SOC and PT
Treatment emergent SAE related to IMP as per Investigator's judgment	Primary SOC and PT
Treatment emergent SAE related to tusamitamab ravtansine as per Investigator's judgment	Primary SOC and PT
Treatment emergent SAE related to pembrolizumab as per Investigator's judgment	Primary SOC and PT
Treatment emergent SAE related to cisplatin as per Investigator's judgment	Primary SOC and PT
Treatment emergent SAE related to carboplatin as per Investigator's judgment	Primary SOC and PT
Treatment emergent SAE related to pemetrexed as per Investigator's judgment	Primary SOC and PT
TEAE leading to permanent full study intervention discontinuation	Primary SOC and PT
TEAE leading to permanent partial discontinuation of tusamitamab ravtansine	Primary SOC and PT
TEAE leading to permanent partial discontinuation of pembrolizumab	Primary SOC and PT
TEAE leading to permanent partial discontinuation of cisplatin	Primary SOC and PT
TEAE leading to permanent partial discontinuation of carboplatin	Primary SOC and PT
TEAE leading to permanent partial discontinuation of pemetrexed	Primary SOC and PT
TEAE leading to death (death as an outcome of the AE as reported by the Investigator in the AE page)	Primary SOC and PT
TEAE related to tusamitamab ravtansine and leading to death (death as an outcome of the AE as reported by the Investigator in the AE page)	Primary SOC and PT
Pre-treatment AE	Overview[a]
	Primary SOC and PT
Pre-treatment SAE	Primary SOC and PT
Post-treatment AE	Overview[a]
	Primary SOC and PT
Post-treatment SAE	Primary SOC and PT

Type of AE	MedDRA levels
TEAE leading to dose modification of tusamitamab ravtansine (including dose delay, dose reduction and dose omission)	Primary SOC and PT
TEAE leading to dose modification of pembrolizumab (including dose delay and dose omission)	Primary SOC and PT
TEAE leading to dose modification of cisplatin (including dose delay, dose reduction and dose omission)	Primary SOC and PT
TEAE leading to dose modification of carboplatin (including dose delay, dose reduction and dose omission)	Primary SOC and PT
TEAE leading to dose modification of pemetrexed (including dose delay, dose reduction and dose omission)	Primary SOC and PT
TEAE leading to dose interruption of tusamitamab ravtansine	Primary SOC and PT
TEAE leading to dose interruption of pembrolizumab	Primary SOC and PT
TEAE leading to dose interruption of cisplatin	Primary SOC and PT
TEAE leading to dose interruption of carboplatin	Primary SOC and PT
TEAE leading to dose interruption of pemetrexed	Primary SOC and PT

a Will include the following AE categories: any AEs, any serious AEs, any AEs leading to death, any AEs leading to permanent full intervention discontinuation.

Analysis of deaths

In addition to the analyses of deaths included in Table 10, the number (%) of participants in the following categories will be provided:

- Deaths during the treatment-emergent and post-treatment periods by study period and main reason for death
- Summary of fatal AEs, by primary SOC and PT:
  - In context of disease progression (death within 30 days from last study intervention administration and the cause of death is disease progression).
  - In context other than disease progression (death within 30 days from last study intervention administration and for whom cause of death is not disease progression or the death occurred more than 30 days from last study intervention administration and the cause of death is AE).
- An overview of Grade 5 AEs will be provided with the following categories:
  - Grade 5 AE (TEAE and post-treatment)
  - Fatal TEAE (regardless of date of death/period)
    - Grade 5 TEAE with a fatal outcome during the treatment-emergent period
    - Any Grade TEAE with a fatal outcome during the post-treatment period
  - Post-treatment Grade 5 AE (excluding a TEAE that worsened to Grade 5 during the post-treatment period)
- Deaths in non-enrolled participants or enrolled but not treated participants

Analysis of adverse events of special interest (AESIs) and other AEs of interest

Adverse events of special interest (AESIs) and other AEs of interest will be selected for analyses as indicated in Table 11. Number (%) of participants experiencing at least one event will be provided for each event of interest, by PT (if applicable). Tables will be sorted as indicated in Table 9.

Table 11 - Selections for AESIs and other AEs of interest

AESIs and other AEs of interest	Selection
AESIs	
Grade ≥3 keratopathy	e-CRF AESI specific tick box on the AE page. It could include Grade ≥3 events with PTs from CMQ of corneal events
Bundle branch blocks or any conduction defects	e-CRF AESI specific tick box on the AE page. It could include events with PTs from SMQ "Conduction defects"
Grade ≥3 liver enzyme increased (symptomatic or asymptomatic)	e-CRF AESI specific tick box on the AE page. It could include Grade ≥3 events with the following PTs: "Alanine aminotransferase increased", "Aspartate aminotransferase increased", "Transaminases increased", "Hepatic function abnormal", "Hepatic enzyme increased", "Liver function test increased", "Transaminases abnormal", "Hepatic enzyme abnormal", or "Liver function test abnormal"
Symptomatic overdose (serious or nonserious) with IMP/NIMP	e-CRF symptomatic overdose specific tick box on the Overdose page
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	eCRF specific tick box for adverse event linked to pregnancy on the Pregnancy page
Other AEs of interest	
Any AE meeting DLT criteria	AEs reported on the e-CRF DLT page outside the DLT observation period
Corneal events	CMQ "Corneal events compound level" containing the PTs included in both SOC "Eye disorders" and SMQ "Corneal disorders" (Narrow)
Ocular/visual symptoms (excluding corneal disorders)	CMQ "Eye disorders exclude corneal disorders" containing PTs included in SOC "Eyes disorders" and excluding PTs in SMQ "Corneal disorders" (Narrow)
Cardiac conduction defects	SMQ "Conduction defects" (Narrow)
Peripheral neuropathy events	SMQ "Peripheral neuropathy" (Narrow and Broad)
Gastrointestinal disorders	CMQ "Bowel disorders" (see Section 5.6)[a]
Infusion allergic reactions	SMQ "Hypersensitivity" (Narrow) and adverse event occurring on the day or the day after infusion
Hepatic disorders events	SMQ "Hepatic Disorders" (Narrow and Broad)
Hematological events	SMQ "Haematopoietic cytopenias" (Narrow and Broad)
AE related to COVID-19 illness	SMQ "COVID-19" (Narrow)

a The list of terms may be adjusted according to MedDRA version changes

An overview of corneal TEAE will be provided with the following AE categories: any corneal TEAE, Grade ≥3 corneal TEAE, treatment-emergent corneal SAE, corneal TEAE leading to permanent full intervention discontinuation, corneal TEAE leading to permanent partial discontinuation of tusamitamab ravtansine, corneal TEAE related to IMP, Grade ≥3 corneal TEAE related to IMP, and corneal TEAE leading to dose modification of tusamitamab ravtansine.

In addition, descriptive analyses will be provided on ocular/visual symptoms reported as associated with the corneal adverse events. These analyses will be performed based on the Investigator's reporting of ocular toxicities (using Investigator's terms collected in the category "Ocular/visual symptoms" in the AE page and using associated symptoms reported in the ocular/visual symptoms page during each corneal event). A summary of treatment-emergent corneal events will be provided.

- Number (%) of participants by worst grade
- Cycle of first onset of corneal event regardless of the grade
- Cycle of first onset of corneal event with the worst grade
- Relationship to the study intervention: in case of multiple events with different relationships, if any event is related, then the relationship will be considered as related
- Action taken with the study intervention: in case of multiple events with different actions, the most severe action taken will be tabulated and selected according to the following order of severity: drug withdrawn, dose reduced, drug interrupted, dose not changed
- Outcome: in case of multiple events with different outcomes, the most severe outcome will be tabulated and selected according to the following order of severity: fatal, not recovered or resolved, recovering or resolving, recovered or resolved with sequelae, recovered or resolved, unknown

In addition, analyses on occurrence and recurrence of corneal events will be provided. An occurrence of corneal event is defined as one or a group of concomitant corneal events. A recurrence is defined as any new occurrence of corneal event starting after a previous resolved occurrence.

- The number of occurrences by participant
- The time to first onset of corneal event will be described using Kaplan-Meier curves. Time to first onset is defined as the time from the date of first IMP administration to the date of the first occurrence of the event. In the absence of an event before the analysis cut-off date, it will be censored at the end date of the treatment-emergent period, analysis cut-off date or date of death, whichever occurs first.
- The time to recovery will be summarized using descriptive statistics in participants who have had at least one recovered or resolved occurrence of corneal event (with or without sequelae), considering the longest duration, and the longest duration of the worst grade among all occurrences by participant.
- The time to recurrence will be summarized using descriptive statistics in participants who have had at least one recurrence, considering the shortest time among all recurrences by participant.

4.7.3 Additional safety assessments

4.7.3.1 Laboratory variables, vital signs and electrocardiograms (ECGs)

The following laboratory variables, vital signs and electrocardiogram (ECG) variables will be analyzed. They will be converted into standard international units.

- Hematology and coagulation:
  - Red blood cells and platelets and coagulation: hemoglobin, hematocrit, platelet count and prothrombin time (expressed as international normalized ratio [INR]).
  - White blood cells: white blood cell (WBC) count, neutrophils, lymphocytes, monocytes, basophils and eosinophils.
- Clinical chemistry:
  - Metabolism: glucose, total protein and albumin.
  - Electrolytes: sodium, potassium, chloride, phosphate and corrected calcium. Corrected calcium (mmol/L) will be derived using the following formula: measured total calcium (mmol/L) + 0.8 x 0.25 x (4.0 - [serum albumin (g/L) x 0.1]), where 4.0 represents the average albumin level.
  - Renal function: creatinine, blood urea nitrogen (BUN), urea.
  - Liver function: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), total and conjugated bilirubin.
  - Thyroid function: thyroid-stimulating hormone (TSH), total or free tri-iodothyronine (T3) and free thyroxine (FT4)
  - Circulating carcinoembryonic antigen (CEA)
- Vital signs: pulse rate, systolic and diastolic blood pressure, weight and ECOG Performance Status (PS).
- ECG variables: heart rate, PR, QRS, QT, and corrected QTc (according to Fridericia).

Data below the lower limit of quantitation/detection limit (LLOQ) will be replaced by half of the LLOQ, data above the upper limit of quantification will be replaced by ULOQ value.

For hematological parameters and some selected coagulation and biochemistry parameters, Sanofi sponsor generic ranges (LLN, ULN) are defined and will be used for grading (see list of parameters in Section 5.5). For other coagulation and biochemistry parameters, grading will be derived using local laboratory normal ranges.

Quantitative analyses

For vital signs and ECG variables above, descriptive statistics for results and changes from baseline for each planned visit, and the worst value (minimum and/or maximum value depending on the parameter) during the treatment-emergent period will be provided. These analyses will be performed using local measurements.

For QRS and QTc variables, blood pressure, and heart rate, mean changes from baseline with the corresponding standard error will be plotted over time.

Analyses according to potentially clinically significant abnormalities (PCSA) and NCI grading

For laboratory variables, analyses according to NCI grading will be made based on NCI-CTCAE Version 5.0. In addition, for laboratory variables for which NCI-CTCAE scale is not applicable, vital signs and ECG variables, PCSA analyses will be performed based on the PCSA list currently in effect at Sanofi at the time of the database lock.

Analyses according to PCSA and NCI grading will be performed based on the worst value during the treatment-emergent period, using all measurements (either local or central, either scheduled, nonscheduled or repeated).

For laboratory variables, vital signs and ECG variables above, the incidence of participants with at least one PCSA during the treatment-emergent period will be summarized regardless of the baseline level and according to the following baseline status categories:

- Normal/missing
- Abnormal according to PCSA criterion or criteria

For laboratory variables graded by NCI-CTCAE,

- The number (%) of participants with abnormal laboratory tests at baseline will be presented by grade.
- The number (%) of participants with abnormal laboratory tests during the treatment-emergent period will be summarized by grade. When appropriate, the number (%) of participants with abnormality of any grade and with Grade 3-4 abnormalities will be provided.

For laboratory variables not graded by NCI-CTCAE nor by PCSA, the number (%) of participants with laboratory tests outside normal ranges will be provided.

Additional analyses for drug-induced liver injury

The following additional analyses will be performed for drug-induced liver injury:

- A graph of the distribution of peak values of ALT versus peak values of total bilirubin during the treatment-emergent period will be provided.
- For each liver function test (eg, ALT), participants having experienced a PCSA (eg, ALT >5 ULN) will be summarized using the following categories: Returned to baseline PCSA status (or returned to value ≤ ULN in case of missing baseline) before last IMP dose, Returned to baseline PCSA status after last IMP dose, Never returned to baseline PCSA status, No assessment after elevation. This summary will be performed by categories of elevation (ALT >3, >5, >10, >20 ULN).

4.7.3.2 Ocular examinations

Schirmer test

Participants reported Schirmer's test will be classified into 3 classes at baseline: normal ≥15 mm, mild 15-5 mm, severe <5 mm. The worst classification between the laterality will be considered. The number (%) of participants by baseline status will be provided for participants with keratopathy/keratitis and for participants without event.

Descriptive statistics on the changes from baseline at the time the keratopathy/keratitis (CMQ) occurred will be displayed.

Visual acuity test

Descriptive statistics on the changes from baseline at the time the keratopathy/keratitis (CMQ) occurred will be displayed.

Slit lamp examination

For participants experiencing keratopathy/keratitis (CMQ), descriptive statistics will be provided describing the type of lesions and the distribution.

4.8 OTHER ANALYSES

4.8.1 PK analyses

PK analyses will be performed on the PK population as defined in Section 3.

4.8.1.1 Tusamitamab ravtansine, pembrolizumab, cisplatin, carboplatin and pemetrexed

Individual concentrations will be listed and summarized by dose level (if applicable) and by drug using descriptive statistics (such as the number of observations, arithmetic and geometric means, median, standard deviation, standard error [SE], coefficient of variation [CV], minimum, and maximum).

All concentration values below the LLOQ will be treated as zero in individual listing and respective descriptive statistics.

4.8.1.2 Population PK analysis

This analysis will be performed by PKDM department at Sanofi. Details of the analysis plan will be provided in a separate document.

4.8.1.3 Immunogenicity impact on PK

Immunogenicity impact on PK of tusamitamab ravtansine may be explored, depending on the ATA incidence.

Descriptive statistics of C_{trough} will be provided at each cycle in the subset of negative participants by dose level (if applicable).

The impact of immunogenicity on PK will be assessed graphically by plotting individual C_{trough} profiles of ATA-positive participants along with mean (+/- SD) C_{trough} profile of ATA-negative participants by dose level. In this plot, concentrations obtained at the time of an ATA-positive result will be highlighted.

4.8.2 Immunogenicity analyses

A summary table with number (%) of participants with pre-existing ATA, number (%) of participants with treatment-boosted ATA, number (%) of ATA-negative participants at baseline, number (%) of participants with treatment-induced ATA (either transient, persistent or indeterminate) (see definitions below) along with descriptive statistics of titer will be reported by dose level (if applicable) and overall on the ATA population (as defined in Section 3). Number (%) of ATA-positive participants and ATA incidence will also be presented.

For ATA-positive participants, descriptive statistics on time to onset and duration of ATA response will be provided using a summary table.

An individual data listing will be provided for participants having at least one positive or inconclusive ATA sample with study period (cycle), ATA sample study day, tusamitamab ravtansine C_{trough} value, ATA samples result (positive, negative or inconclusive), ATA samples titer (if applicable), ATA participant status (positive, negative or inconclusive) and ATA participant response (kinetic of the immune response: indeterminate, transient or inconclusive).

Note that treatment-boosted ATA are excluded from the analyses of ATA kinetics because this type of immune response differs mechanistically.

The impact on safety and efficacy endpoints may be further explored by graphical methods or descriptively, depending on the ATA incidence.

ATA endpoint

Anti-therapeutic antibodies are biologic drug-reactive antibody, including pre-existing host antibodies that are cross-reactive with the administered biotherapeutic (baseline ATA).

ATA attributes

Pre-existing ATA is defined as ATA reactive with the biotherapeutic present in participants before first administration of intervention (or before initiation of the clinical study).

Treatment-boosted ATA is defined as pre-existing ATA that was boosted to a higher-level following administration of biotherapeutic (ie, any time after the initial drug administration) the ATA titer is significantly higher than the baseline titer. A low serial dilution schema (2-fold or 3-fold) should be applied during titration. A difference in titer values of two titer steps between treatment or follow-up sample and its baseline sample is considered significant. For examples, at least a 4-fold increase in titers for 2-fold serial dilution schema (or 9-fold increase in titers for 3-fold serial dilution schema). If no titer could be determined for a positive sample, the titer will be reported as the minimal required dilution of the assay.

Treatment-induced ATA is defined as ATAs developed de novo (seroconversion) following administration of the biotherapeutic (ie, formation of ATAs any time after the initial drug administration in a participant without pre-existing ATAs). If the baseline ATA sample is missing or non-reportable and at least one reportable ATA sample is available during the treatment (including follow-up period) the baseline sample will be considered as "negative" for data analysis. This is considered being a conservative approach for ATA assessment.

Participant status

Among evaluable population for immunogenicity (described in Section 3), following participant status will be defined:

- **ATA-positive** participant: A participant with at least one treatment-induced or treatment-boosted ATA-positive sample at any time during the treatment or follow-up observation period.
- **ATA-negative** participant: Participant without any treatment-induced or treatment-boosted ATApositive sample during the treatment or follow-up observation period.
- **ATA-inconclusive** participant: A participant who cannot irrefutably be classified as ATA negative (eg, all post baseline samples inconclusive).

Overview of the ATA response

- The term **ATA incidence** only defines the proportion of subjects found to either have seroconverted (treatment-induced ATAs) or boosted their pre-existing ATA response during the study. Only evaluable subjects (described in Section 3) are considered for computing ATA incidence.

Kinetics of the immune response

- **Onset of ATA:** refers to the time period between the initial drug administration and the first instance of treatment-induced ATAs. The use of real-elapsed days should be used for the calculations. The "median time to ATA development" and the quartiles Q1 and Q3 should be reported.
- **Duration of ATA:** ATA duration will be calculated as the date of last treatment-induced ATA sample minus date of first treatment-induced or treatment-boosted ATA sample +1; ATA duration will be calculated only for participants with at least two ATA positive samples. Median duration of an induced ATA response and the quartiles Q1 and Q3 should be reported.

- **Transient ATA response** is defined by:
  - Treatment-induced ATA detected only at one sampling time point during the treatment or follow-up observation period (excluding the last sampling time point), OR
  - Treatment-induced ATA detected at two or more sampling time points during the treatment (including follow-up period if any), where the first and last ATA-positive samples (irrespective of any negative samples in between) are separated by a period less than 16 weeks, and the participant's last sampling time point is ATA negative.
- **Persistent ATA response** is defined by:
  - Treatment-induced ATA detected at two or more sampling time points during the treatment (including follow-up period if any), where the first and last ATA-positive samples are separated by at least 16 weeks (irrespective of any negative samples in between).
- **Indeterminate ATA** is defined by:
  - Treatment-induced ATA detected only at the last sampling time point, OR
  - The last two samples being ATA-positive and separated by a period of less than 16 weeks.

4.8.3 Biomarkers analyses

Several exploratory objectives related to pharmacodynamic/genomic endpoints will be considered in this study.

Unless otherwise specified, biomarkers analyses will be performed on participants with available data from the all-treated population.

4.8.3.1 Circulating CEA

The circulating CEA will be considered as a quantitative variable or as a binary variable when considering different binary thresholds: <3, <5, <50, <80 or <100 µg/L.

Circulating CEA values below the LLOQ will be replaced by half of the LLOQ.

4.8.3.1.1 Circulating CEA levels at pre-screening

Biomarkers analyses described in this section will be performed on participants with available data from the pre-screening population.

The circulating CEA levels at pre-screening will be presented using descriptive statistics.

The association between the circulating CEA at pre-screening and the CEACAM5 expression from archival or fresh tumor tissue (IHC) may also be assessed. To this end, Pearson correlation, Spearman's rank, or Kendall's tau coefficient will be considered depending on the nature of the

data. The time from tumor biopsies and pre-screening will be also described and investigated in the correlation between pre-screening circulating CEA levels and IHC CEACAM5 expression.

4.8.3.1.2 Modulations of circulating CEA as a potential PD biomarker of response to tusamitamab ravtansine treatment

The circulating CEA at different timepoints and its relative change from baseline will be presented using descriptive statistics by response status and overall.

The association between the circulating CEA at baseline and the CEACAM5 expression on tumor tissue (% of tumor cells expressing CEACAM5 at intensity ≥2+) may also be assessed. To this end, Pearson correlation, Spearman's rank or Kendall's tau coefficient will be considered depending on the nature of the data. The circulating CEA at baseline may also be associated with the baseline tumor burden considered as the sum of the longest diameters of the target lesions at baseline.

The association between the circulating CEA at baseline and confirmed objective response per RECIST 1.1 may be assessed using a logistic regression model and providing prognostic effect (ie, main effect: overall effect of the circulating CEA level on the efficacy endpoint).

4.8.3.2 Circulating free DNA

4.8.3.2.1 Relationship between the tumor mutation profiles detected in the cfDNA at baseline with efficacy outcomes

Descriptive statistics of the number of participants with mutations at baseline for each gene will be presented by response status, overall and possibly according to other demographic characteristics. Statistical testing to evaluate the association with the confirmed objective response may be implemented for genes with more than 5 participants with mutations. If needed, multiple testing correction using Benjamini-Hochberg method may be used to control the false discovery rate (FDR).

4.8.3.2.2 Changes in cfDNA in response to tusamitamab ravtansine treatment

The evolution between Cycle 1 Day 1 and Cycle 5 Day 1 of the number of participants with mutations for each gene will be described using descriptive statistics by response status and overall. For key genes of interest, the mutation allele frequency will be described at Cycle 1 Day 1, Cycle 5 Day 1 in addition to the relative change from baseline, and visualize through graphical visualization method.

4.8.3.3 CEACAM5 expression on circulating tumoral cells (CTCs)

CEACAM5 expression on CTCs may be considered as a quantitative or categorical variable and will be presented using descriptive statistics.

The correlation between the CEACAM5 expression on CTCs and the CEACAM5 expression on tumor tissue may be assessed using Pearson correlation, Spearman's rank or Kendall's tau coefficient depending on the nature of the data.

4.9 INTERIM ANALYSES

No formal interim analysis is planned in this study.

The study analysis will be conducted in three steps.

The first analysis step will be conducted when the last participant treated to determine the RP2D in Part A, Part B or Part C has ended Cycle 1.

The second analysis step will be conducted when all treated participants have had at least 2 post-baseline tumor assessments, experienced confirmed objective response, or have discontinued the study for any reason. This study cut-off will occur approximately 4.5 months after the date of the first IMP administration of the last participant: 3 months for 2 tumor assessments and 1.5 months if a confirmation of response is needed. All analyses will be updated at this time.

The final analysis will be conducted at the end of the study. Only safety analyses will be updated at this time.

For each analysis step, the analysis cut-off date will be defined as the date of the database extraction that will be performed for the analysis after the cut-off (study cut-off for the first and second analysis steps).

Analyses methods and conventions described in the other sections of this SAP will be applied for all analyses as applicable. The following additional rules will apply for the first and second analysis steps:

- Participants without end of treatment status performed at the time of the analysis cut-off date will be considered as ongoing. Therefore:
  - Participants who did not discontinue the study intervention at analysis cut-off date will be analyzed as "ongoing" in the disposition summary.
  - Their treatment-emergent (TE) period and concomitant medication period will end at the analysis cut-off date.

5 SUPPORTING DOCUMENTATION

5.1 APPENDIX 1 LIST OF ABBREVIATIONS

ADI:	actual dose intensity
AE:	adverse event
AESI:	adverse event of special interest
ALP:	alkaline phosphatase
ALT:	alanine aminotransferase
AST:	aspartate aminotransferase
ATA:	anti-therapeutic antibody
BOR:	best overall response
BUN:	blood urea nitrogen
CEA:	carcinoembryonic antigen
CEACAM5:	carcinoembryonic antigen-related cell adhesion molecule 5
cfDNA:	circulating free deoxyribonucleic acid
CMQ:	company MedDRA queries
COVID-19:	coronavirus disease 2019
CR:	complete response
CTC:	circulating tumoral cell
CTCAE:	common terminology criteria for adverse events
CV:	coefficient of variation
DLT:	dose-limiting toxicity
ECG:	electrocardiogram
ECOG:	Eastern Cooperative Oncology Group
e-CRF:	electronic case report form
EOT:	end of treatment
FT4:	free thyroxine
HLGT:	high-level group term
HLT:	high-level term
IHC:	immunohistochemistry
IMP:	investigational medicinal product
INR:	international normalized ratio
LDH:	lactate dehydrogenase
LLN:	lower limit of normal
LLOQ:	lower limit of quantitation
LLT:	lower-level term
MedDRA:	medical dictionary for regulatory activities
NCI:	National Cancer Institute
NSQ NSCLC:	non-squamous non-small cell lung cancer
ORR:	objective response rate
PCSA:	potentially clinically significant abnormalities
PD:	pharmacodynamic
PDI:	planned dose intensity

PK: pharmacokinetics
PR: partial response
PS: performance status
PT: preferred term
RDI: relative dose intensity
RECIST: response evaluation criteria in solid tumors
RP2D: recommended phase 2 dose
SAE: serious adverse event
SAP: statistical analysis plan
SD: standard deviation
SE: standard error
SMQ: standardized MedDRA queries
SOC: system organ class
T3: tri-iodothyronine
TE: treatment-emergent
TEAE: treatment-emergent adverse event
TSH: thyroid stimulating hormone
ULN: upper limit of normal
ULOQ: upper limit of quantitation
WHO-DD: World Health Organization-drug dictionary

5.2 APPENDIX 2 CHANGES TO PROTOCOL-PLANNED ANALYSES

This section summarizes major statistical changes in the protocol amendments.

Table 12 - Major statistical changes in protocol amendments

Amendment Number	Approval Date	Changes	Rationale
1	23-Nov-2020	Added objectives and endpoints, statistical populations, and statistical analyses for Part B.	To reflect the change of adding the combination arm of tusamitamab ravtansine in combination with pembrolizumab and platinum-based chemotherapy as Part B, in order to evaluate the safety of the combination.
		Added a dose level of 170 mg/m^2 Q3W to be evaluated in Part 1 of Part A Updated sample size in Part A	Decision based on data from the 170 mg/m^2 Q3W cohort in study TED13751.
		Added possible interim analysis for Part A when study cut-off for primary analysis of Part B is reached.	To permit strategic project decision.

Amendment Number	Approval Date	Changes	Rationale
2	25-Jan-2021	No major statistical changes	
3	04-May-2021	Removed objectives and endpoints of pembrolizumab single agent arm in Part A Removed randomization in Part A Remove PD-L1 requirement for Part A Update sample size and statistical population in Part A Remove blinding considerations. Remove interim analysis planned in Part A.	To reflect the change of removing pembrolizumab alone arm in Part A.
4	26-Jul-2021	Move anti-tumor activity of tusamitamab ravtansine in combination with pembrolizumab from primary endpoint to secondary endpoint. Decrease the sample size in Part A to get approximately the same number of participants treated at the recommended dose in each Part. Removed DOR and PFS from secondary endpoint analysis from Part A. Removed ORR per iRECIST from exploratory endpoints from Part A. Removed activity population.	Primary objective of Part A is to assess the tolerability of the combination and to determine the recommended dose as for the other parts.
		Added objectives and endpoints, statistical populations, and statistical analyses 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.
		Non-compartmental analysis replaced by population PK analysis.	To reflect the change in PK analysis strategy.

5.3 APPENDIX 3 DEMOGRAPHICS AND BASELINE CHARACTERISTICS, PRIOR OR CONCOMITANT MEDICATIONS

Demographics, baseline characteristics, medical surgical history

The following demographics and baseline characteristics, medical and surgical history and disease characteristics at baseline will be summarized using descriptive statistics in the all-treated population.

Demographic and baseline characteristics:

- Age in years as quantitative variable and in categories (<65, [65-75], ≥75)
- Sex (Male, Female)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Not reported, Unknown)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino, Unknown)
- ECOG PS (0, 1)
- Weight in kg as quantitative variable
- BSA in m^2 as quantitative variable

Baseline safety and efficacy parameters (apart from those listed above) will be presented along with the safety and efficacy summaries.

Medical (or surgical) history includes relevant history of previous pathologies and surgeries. Medical and surgical history will be coded to a LLT, PT, HLT, HLGT, and associated primary SOC using the MedDRA version currently in effect at Sanofi at the time of database lock.

Specific disease history includes primary tumor site, histopathology type, staging, time from initial diagnosis to first administration of IMP (in months).

Specific disease status at study entry includes extent of diseases, number and type of organs involved (including primary tumor location), PD-L1 expression (<1%, ≥1% and <1%, 1-49% and ≥50%), circulating CEA (<100 µg/L, ≥100 µg/L and <80 µg/L, ≥80 µg/L), smoking status (current, former, never), smoking habits (in pack-years).

Prior or concomitant medications

All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) using the version currently in effect at Sanofi at the time of database lock.

- Prior medications are those the participant received prior to first IMP intake. Prior medications can be discontinued before first administration or can be ongoing during treatment period.
- Concomitant medications are any medications received by the participant concomitantly to any IMP from the first administration of IMP to the last IMP intake + 30 days.
- Post-treatment medications are those the participant received in the period running from the end of the concomitant medications period up to the end of the study.
- A given medication can be classified as a prior medication and/or as a concomitant medication and/or as post-treatment medication. If it cannot be determined whether a given medication was received prior or concomitantly or post, it will be considered as prior, concomitant, and post-treatment medication.

The prior and concomitant medications will be summarized on the all-treated population, by anatomic and therapeutic level. Participants will be counted once in each ATC category (anatomic or therapeutic) linked to the medication.

Premedications

As defined in Section 6.1 of the study protocol, participants receive premedications prior to tusamitamab ravtansine infusion to prevent from infusion related allergic reactions and vitamin supplementation for pemetrexed. Premedications are defined as non-investigational medicinal products and are reported on a specific e-CRF page.

To summarize premedications prior to tusamitamab ravtansine, number (%) of participants treated with dexamethasone and number (%) of participants treated with Histamine H1 antagonist after 4 cycles will be provided. In addition, number of cycles of participants treated with Histamine H1 antagonist will be summarized as a quantitative variable.

In addition, for Part C, to summarize premedications prior to pemetrexed, number (%) of participants who received Folic Acid, number (%) of participants who received Vitamin B12 and number (%) of participants treated with dexamethasone will be provided.

Anticancer therapies

Prior anticancer therapies include chemotherapy, surgery and radiotherapy.

- Prior chemotherapy: number (%) of participants with prior chemotherapy including neoadjuvant/adjuvant treatment, number (%) of participants with intent: neoadjuvant, adjuvant and time from completion of last chemotherapy to first administration of IMP (in months).
- Prior surgery: number (%) of participants with any prior surgery related to lung cancer, type of surgery and time from the last surgery to first administration of IMP (in months).
- Prior radiotherapy: number (%) of participants with any prior radiotherapy related to lung cancer, intent, analgesic intent if palliative and time from last dose of radiotherapy to first administration of IMP (in months).

Further anticancer therapies (including systemic anticancer therapies, surgeries and radiotherapies) after discontinuation of study intervention will be summarized based on WHO-DD coding.

5.4 APPENDIX 4 DATA HANDLING CONVENTIONS

Unscheduled visits

Unscheduled visit measurements will be used for computation of baseline and worst treatment-emergent values and/or grades.

Unscheduled tumor assessments will be used for computation of efficacy endpoints based on radiological assessments of tumor burden.

5.5 APPENDIX 5 SANOFI SPONSOR GENERIC RANGES FOR HEMATOLOGICAL AND BIOCHEMISTRY PARAMETERS

The current list of generic ranges (for adults) for hematological, coagulation and biochemistry parameters (3) are provided in tables below.

Table 13 - Generic ranges for hematological and coagulation parameters

Parameter	Gender	Unit	LLN	ULN
Basophils		10^9/L	0	0.15
Eosinophils		10^9/L	0	0.4
Hematocrit	M	Ratio	0.41	0.53
Hematocrit	F	Ratio	0.36	0.46
Hemoglobin	M	g/L	135	175
Hemoglobin	F	g/L	120	160
Leukocytes (WBC) count		10^9/L	4.5	11
Lymphocytes		10^9/L	1	2
Monocytes		10^9/L	0.18	0.5
Neutrophils		10^9/L	1.8	3.15
Platelets count		10^9/L	150	350
Prothrombin time		INR	0.8	1.2

Table 14 - Generic ranges for biochemistry parameters

Parameter	Unit	LLN	ULN
Albumin	g/L	35	55
Blood Urea Nitrogen	mmol/L	3.6	7.1
Corrected calcium	mmol/L	2.2	2.6
Glucose	mmol/L	3.9	7
Chloride	mmol/L	80	115
Potassium	mmol/L	3.5	5
Sodium	mmol/L	-136	145
Phosphate	mmol/L	1	1.4
Protein	g/L	55	80
Urea	mmol/L	3.6	7.1

5.6 APPENDIX 6 LIST OF TERMS IN COMPANY MEDDRA QUERIES (CMQ)

The following CMQ are using MedDRA Version 24.1.

- CMQ “Bowel disorders” is based on the primary SOC “Gastrointestinal disorders” and the following HLGTs:
  - Anaemias nonhaemolytic and marrow depression
  - Anal and rectal conditions NEC
  - Aneurysms and artery dissections
  - Appetite and general nutritional disorders
  - Bacterial infectious disorders
  - Benign neoplasms gastrointestinal
  - Bile duct disorders
  - Blood and lymphatic system disorders congenital
  - Bone disorders (excl congenital and fractures)
  - Bronchial disorders (excl neoplasms)
  - Cardiac and vascular disorders congenital
  - Cardiac disorders, signs and symptoms NEC
  - Changes in physical activity
  - Chlamydial infectious disorders
  - Chromosomal abnormalities, gene alterations and gene variants
  - Congenital and hereditary disorders NEC
  - Connective tissue disorders (excl congenital)
  - Cornification and dystrophic skin disorders
  - Cutaneous neoplasms benign
  - Decreased and nonspecific blood pressure disorders and shock
  - Diverticular disorders
  - Eating disorders and disturbances
  - Endocrine and glandular disorders NEC
  - Endocrine neoplasms benign
  - Endocrine neoplasms malignant and unspecified
  - Epidermal and dermal conditions
  - Exposures, chemical injuries and poisoning
  - Food intolerance syndromes
  - Fungal infectious disorders
  - Gastrointestinal conditions NEC
  - Gastrointestinal haemorrhages NEC
  - Gastrointestinal infections
  - Gastrointestinal inflammatory conditions

- Gastrointestinal investigations
- Gastrointestinal motility and defaecation conditions
- Gastrointestinal neoplasms benign
- Gastrointestinal neoplasms malignant and unspecified
- Gastrointestinal signs and symptoms
- Gastrointestinal stenosis and obstruction
- Gastrointestinal tract disorders congenital
- Gastrointestinal ulceration and perforation
- Gastrointestinal vascular conditions
- General system disorders NEC
- Haemolyses and related conditions
- Helminthic disorders
- Hepatic and hepatobiliary disorders
- Immune disorders NEC
- Immune system disorders congenital
- Infections - pathogen unspecified
- Injuries NEC
- Injuries by physical agents
- Inner ear and VIIIth cranial nerve disorders
- Joint disorders
- Lymphomas non-Hodgkin's B-cell
- Lymphomas non-Hodgkin's unspecified histology
- Malabsorption conditions
- Malignant and unspecified neoplasms gastrointestinal NEC
- Maternal complications of pregnancy
- Mesotheliomas
- Metabolic and nutritional disorders congenital
- Metastases
- Miscellaneous and site unspecified neoplasms malignant and unspecified
- Movement disorders (incl parkinsonism)
- Muscle disorders
- Musculoskeletal and connective tissue disorders NEC
- Musculoskeletal and connective tissue disorders congenital
- Mycobacterial infectious disorders
- Mycoplasmal infectious disorders
- Neuromuscular disorders
- Procedural related injuries and complications NEC
- Prostatic disorders (excl infections and inflammations)

- Protozoal infectious disorders
- Psychiatric disorders NEC
- Reproductive tract and breast disorders congenital
- Reproductive tract disorders NEC
- Respiratory and mediastinal neoplasms benign (excl mesotheliomas)
- Respiratory and mediastinal neoplasms malignant and unspecified
- Respiratory disorders congenital
- Respiratory tract signs and symptoms
- Skin and subcutaneous tissue disorders congenital
- Skin vascular abnormalities
- Soft tissue neoplasms malignant and unspecified
- Somatic symptom and related disorders
- Spleen, lymphatic and reticuloendothelial system disorders
- Tissue disorders NEC
- Upper respiratory tract disorders (excl infections)
- Urinary tract signs and symptoms
- Vascular disorders NEC
- Viral infectious disorders
- Vitamin related disorders

6 REFERENCES

1. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst. 2000;92(3):205-16.

2. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47.

3. Kratz A, Ferraro M, Sluss PM, Lewandrowski KB. Laboratory reference values. N Engl J Med. 2004;351(15):1548-63.

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