# STATISTICAL ANALYSIS PLAN

| | |
|---|---|
| **Protocol title:** | **A Phase 2 non-randomized, open-label, multi-cohort, multi-center study assessing the clinical benefit of SAR444245 (THOR-707) combined with other anticancer therapies for the treatment of participants with head and neck squamous cell carcinoma (HNSCC) (Pegathor Head and Neck 204)** |
| **Protocol number:** | **ACT16903** |
| **Compound number (INN/Trademark):** | **SAR444245 (Not applicable)** |
| **Study phase:** | **Phase 2** |
| **Short Title:** | **A study of SAR444245 combined with other anticancer therapies for the treatment of participants with HNSCC** |
| **Statistician:** | [redacted] **(contractor, IT&M Stats)** |
| **Statistical project leader:** | [redacted] |
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## TABLE OF CONTENTS

## LIST OF TABLES

# VERSION HISTORY

This statistical analysis plan (SAP) for study ACT16903 is the first version and is based on the amended protocol 03 dated 22-Dec-2021. This section summarizes the major changes to the statistical analysis features in the SAP.

The first participant was enrolled on 19-Oct-2021. This SAP is approved before the first interim analysis.

**Major changes in statistical analysis plan**

| SAP Version | Approval Date | Changes | Rationale | Change from |
|---|---|---|---|---|
| 1 | Current version | • Estimand framework has been added for the primary and main secondary efficacy endpoints. | • To further characterize the antitumor activity effect that will be estimated. | • Amended protocol 03 |

# 1 INTRODUCTION

Major changes to the protocol-planned analyses are described in Section 3.9.

## 1.1 STUDY DESIGN

This is a Phase 2, multi-cohort, un-controlled, non-randomized, open-label, multi-center study assessing the antitumor activity and safety of SAR444245 combined with other anticancer therapies in participants with HNSCC.

The study consists of a core phase for all cohorts, with a safety run-in and an expansion phase for specific cohorts. The results of an interim analysis after the core phase will decide if the expansion phase will be opened. An overview of the study intervention and disease being treated for each cohort is provided in the table below.

| Cohort | Study intervention | Disease |
|---|---|---|
| A1 | SAR444245 + pembrolizumab | R/M HNSCC treatment-naïve for R/M disease, PD-L1 CPS ≥1 |
| A2 | SAR444245 + cetuximab + pembrolizumab | R/M HNSCC treatment-naïve for R/M disease, PD-L1 CPS ≥1 |
| B1 | SAR444245 + pembrolizumab | R/M HNSCC treated with PD1/PD-L1-based regimen & platinum based regimen after failure of no more than 2 regimens for R/M disease |
| B2 | SAR444245 + cetuximab | R/M HNSCC treated with platinum-based regimen & cetuximab-naïve after failure of no more than 2 regimens for R/M disease |

CPS: combined positive score; HNSCC: Head and neck squamous cell carcinoma ; PD1: Programmed cell death protein 1; PD-L1: programmed cell death-ligand 1; R/M: Recurrent/metastatic.

Participants who are eligible for both Cohorts A1 (to receive SAR444245 and pembrolizumab) and A2 (to receive SAR444245, pembrolizumab and cetuximab) should be enrolled in Cohort A1 until Cohort A1 enrollment is completed, meaning that cohort A2 will start after cohort A1 completion. For each cohort, SAR444245 will be administered at 24 µg/kg Q3W. The level might be reduced to [redacted]µg/kg [redacted] or another lower dose level. Cetuximab will be administered at a dose of 400 mg/m² as an IV infusion on Cycle 1 Day 1 of the study followed by subsequent doses of 250 mg/m² cetuximab IV QW (cohorts A2 and B2). The planned dose of pembrolizumab for this study is 200 mg Q3W (cohorts A1, A2 and B1).

## 1.2 OBJECTIVES AND ENDPOINTS

**Table 1 - Objectives and endpoints**

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • To determine the antitumor activity of SAR444245 in combination with other anticancer therapies in patients with HNSCC | • Objective response rate (ORR) defined as proportion of participants who have a confirmed complete response (CR) or partial response (PR) determined by Investigator per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 (1) |
| **Secondary** | |
| • To assess the safety profile of SAR444245 when combined with other anti-cancer therapies | • Incidence of TEAEs, SAEs, laboratory abnormalities according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) V 5.0 and American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading (2) |
| • To assess other indicators of antitumor activity | • Time to response (TTR) defined as the time from the first administration of investigational medicinal product (IMP) to the first tumor assessment at which the overall response was recorded as PR or CR that is subsequently confirmed and determined by Investigator per RECIST 1.1<br>• Duration of Response (DoR), defined as the time from first tumor assessment at which the overall response was recorded as PR or CR that is subsequently confirmed until documented progressive disease (PD) determined by Investigator per RECIST 1.1 or death from any cause, whichever occurs first<br>• Clinical benefit rate (CBR) including confirmed CR or PR at any time or stable disease (SD) of at least 6 months (determined by investigator per RECIST 1.1)<br>• Progression free survival (PFS), defined as the time from the date of first IMP administration to the date of first documented disease progression determined by Investigator as per RECIST 1.1, or death due to any cause, whichever occurs first |
| • To assess the concentrations of SAR444245 | • Plasma concentration of SAR444245 |
| • To assess the immunogenicity of SAR444245 | • Incidence of anti-drug antibodies (ADAs) against SAR444245 |

| Objectives | Endpoints |
|---|---|
| **Exploratory** | |
| [redacted] | [redacted] |
| [redacted] | [redacted] |

### 1.2.1 Estimands

Primary estimand defined for main efficacy endpoints are summarized in below Table 2. More details are provided in Section 3.

**Table 2 - Summary of primary estimand for main endpoints**

| Endpoint Category (estimand) | Estimands | | | |
|---|---|---|---|---|
| | **Endpoint** | **Population** | **Intercurrent event(s) (IE) handling strategy** | **Population-level summary (Analysis and missing data handling)** |
| **Primary objective: To determine the antitumor activity of SAR444245 in combination with other anti-cancer therapies** | | | | |
| Primary endpoint (estimand 1) | Objective Response (OR) (confirmed CR or PR) | Efficacy | • While not initiating new anti-cancer therapy (NAT)<br>• - Regardless of early IMP discontinuation (treatment policy strategy) | ORR, defined as the percentage of the participants with objective response (CR or PR) as best overall response. The confidence interval (CI) will be calculated using Clopper Pearson methods. |
| **Secondary objective: To assess other indicators of antitumor activity of SAR444245 in combination with other anti-cancer therapies** | | | | |
| Secondary endpoint (estimand 2) | DOR | Responders from efficacy population | • Had NAT not been initiated (hypothetical strategy)<br>• Regardless of early IMP discontinuation (treatment policy strategy)<br>• - Had two or more consecutive tumor assessments not been missed/unevaluable immediately before documented progression or death (hypothetical strategy) | The Kaplan Meier estimate and corresponding CI of DOR at specified time points. The quantiles of DOR and corresponding CI will be calculated from Kaplan Meier method. |
| Secondary endpoint (estimand 3) | PFS | Efficacy | • Had NAT not been initiated (hypothetical strategy)<br>• Regardless of early IMP discontinuation (treatment policy strategy)<br>• - Had two or more consecutive tumor assessments not been missed/unevaluable immediately before documented progression or death (hypothetical strategy) | The Kaplan Meier estimate and corresponding CI of PFS at specified time points. The quantiles of PFS and corresponding CI will be calculated from Kaplan Meier method. |

# 2 ANALYSIS POPULATIONS

The following populations for analyses are defined. Unless otherwise specified, these populations will be applicable for both safety run-in and dose expansion parts. The participants included in the safety run-in part, if fulfilling the inclusion criteria of the expansion part and if the planned dose and dosing schedule are the same as in dose expansion will be included in the analyses of dose expansion.

**Table 3 - Populations for analyses**

| Population | Description |
|---|---|
| Screened | All participants who have given their informed consent. |
| Enrolled | All participants who have given their informed consent and have been allocated to an intervention (by IRT) regardless of whether the intervention was received or not. |
| Exposed | All participants who have given their informed consent and received at least one dose (even incomplete) of IMP (SAR444245 or cetuximab or pembrolizumab). |
| Population without trial impact (disruption) due to COVID-19 | All exposed participants:<br>• without any critical or major deviation related to Coronavirus disease 2019 (COVID19)<br>• and who did not permanently discontinue treatment due to COVID-19<br>• and who did not permanently discontinue study due to COVID-19 |
| Efficacy | All participants from the exposed population with at least one evaluable post-baseline tumor assessment or who permanently discontinued study treatment. |
| DLT-evaluable | All exposed participants in the run-in period who have been treated and observed for at least 21 days. Any participants who have experienced a DLT during DLT observation period will also be DLT-evaluable. |
| Response-evaluable | All participants from efficacy population with an evaluable baseline and at least one evaluable post-baseline tumor assessments. Participants who died from disease progression before any TA will also be response evaluable. |
| Pharmacokinetic (PK) | All participants from exposed population with at least 1 PK concentration available after the first dose of study intervention. |
| ADA | All participants from exposed population with at least 1 ADA result (positive, negative, or inconclusive) after the first dose of study intervention. |
| Pharmacodynamics (PDy) | All participants from the exposed population with at least 1 PDy parameter assessed after the first dose of study intervention. |

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

For any participant enrolled and treated 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.

# 3 STATISTICAL ANALYSES

## 3.1 GENERAL CONSIDERATIONS

In general, continuous data will be summarized using the number of observations available, mean, standard deviation (SD), median, 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 administration of any of the three IMPs (SAR444245 or cetuximab or pembrolizumab). For participants enrolled but not treated, the baseline value is defined as the last available value before enrollment.

Unless otherwise specified, analyses will be performed by cohort, by dose and overall (if applicable). Participants enrolled in the safety run-in part and treated at the RP2D will be included in the analyses of the core phase.

All efficacy analyses will be performed on the efficacy population. Objective Response Rate (ORR), as well as all other response-related efficacy endpoints will be primarily derived using the Investigator's assessment for all cohorts and using Response Evaluation Criteria in Solid Tumor (RECIST 1.1).

Central imaging may be done retrospectively if significant activity is observed
(See Section 3.2.3 for sensitivity analysis).

Confidence intervals will be two-sided 90% CI for efficacy analyses and will be used for descriptive purposes only, without inference.

The BOR is defined as the best overall response observed from the date of first investigational medicinal product (IMP) until disease progression, death, cut-off date or initiation of further anti-cancer therapy, whichever occurs first. Also:

- A PR or a CR must be confirmed on a second imaging done at least 4 weeks apart, in order to confirm the antitumoral response.
- A SD response must be assessed at least 6 weeks after the first IMP administration to be considered as evaluable.

All safety analyses will be performed on the exposed population.

***Analysis period***

The analysis period will be divided into 3 segments:

- The **pre-treatment period** is defined as the time from when the participants give informed consent to the first administration of the IMP.
- The **on-treatment period** (ie, treatment-emergent [TE] period) is defined as the time from the first administration of IMP up to 30 days after the last administration of IMP.

- The **post-treatment period** is defined as the time from the end of the on-treatment period, ie, 31 days after the last administration of IMP.

## 3.2 PRIMARY ENDPOINT(S) ANALYSIS

### 3.2.1 Definition of endpoint(s)

The primary endpoint is the ORR.

The ORR is defined as the proportion of participants who have a BOR (see Section 3.1) as confirmed CR or PR.

### 3.2.2 Main analytical approach

The primary endpoint, ORR, will be analyzed with the estimand 1, introduced in Section 1.2.1, and defined according to the following attributes:

- The endpoint is confirmed objective response (confirmed CR or PR)
- The treatment condition is SAR444245 in combination with other anti-cancer therapies.
- The analysis population is the efficacy population
- Intercurrent events (IE):
  - The new anticancer therapy IE will be handled with the "**while not initiating new anti-cancer therapy"** strategy; confirmed objective response will be assessed based on tumor assessments up to the time of new anticancer therapy.
  - The early IMP discontinuation IE will be handled with the "**treatment policy"** strategy; confirmed objective response will be assessed based on tumor assessments irrespective of IMP discontinuation.
- Population-level summary will include the ORR and CI using the Clopper-Pearson method. In absence of confirmed OR, participants will be considered as non-responders, whatever the reason (including participants with missing or non-evaluable BOR).

### 3.2.3 Sensitivity analysis

Central imaging reading may be done retrospectively if significant activity is observed. Objective response rate (ORR) may be presented based on central imaging assessment, using the same estimand as for the primary analysis.

### 3.2.4 Supplementary analyses

ORR will be presented for the response-evaluable population.

This supplementary analysis will be provided using an estimand defined according to the following attributes:

- The endpoint is ORR.
- The treatment condition is SAR444245 in combination with other anti-cancer therapies.
- The analysis population is the response-evaluable population.
- Intercurrent events and their handling strategy will be the same as for ORR estimand defined in Section 3.2.2.
- Population-level summary will be the same as for ORR estimand defined in Section 3.2.2.

The BOR will also be summarized with descriptive statistics.

## 3.3 SECONDARY ENDPOINT(S) ANALYSIS

The secondary endpoints detailed in this section are the efficacy endpoints. Other secondary endpoints analyses are defined in Section 3.6 (safety), Section 3.7.1.1 (PK) and Section 3.7.1.2 (immunogenicity).

### 3.3.1 Efficacy secondary endpoint(s)

#### *3.3.1.1 Definition of endpoint(s)*

The time to response (TTR) is defined as the time from the first administration of IMP to the first tumor assessment at which the overall response was recorded as PR or CR that is subsequently confirmed.

The duration of response (DOR) will be defined as the time from the first tumor assessment at which the overall response was recorded as CR or PR that is subsequently confirmed until documented PD before the initiation of any subsequent anti-cancer therapy or death due to any cause, whichever occurs first.

The clinical benefit rate (CBR) is defined as the proportion of participants with clinical benefit: confirmed CR or PR as BOR, or SD lasting at least 6 months (overall response recorded as SD at 6 months, ie, 26 weeks or later from first IMP intake, allowing for the ±7 days visit window for tumor assessment scheduled at 27 weeks).

The progression-free survival (PFS) is defined as the time from the date of first IMP administration to the date of the first documentation of objective PD, or death due to any cause, whichever occurs first.

#### *3.3.1.2 Main analytical approach*

The time to response (TTR) will be assessed on the subgroup of participants who have achieved confirmed OR and will be summarized using descriptive statistics.

The analyses of DOR and PFS are based on estimands 2 and 3 introduced in Section 1.2.1, and defined according to the following attributes:

- The endpoints are DOR and PFS.
- The treatment condition is SAR444245 in combination with other anti-cancer therapies.
- The analysis population for DOR corresponds to all participants from the efficacy population who achieve either confirmed PR or confirmed CR.
- The analysis population for PFS corresponds to all participants from the efficacy population.
- Intercurrent events:
  - The new anticancer therapy IE will be handled with the **hypothetical** strategy: DOR and PFS will be assessed based on tumor assessments had a new anticancer therapy not being taken. DOR and PFS will be assessed based on tumor assessments up to the time of new anticancer therapy.
  - The early IMP discontinuation IE will be handled with the **treatment policy** strategy: DOR and PFS will be assessed based on tumor assessments irrespective of IMP discontinuation.
  - Two or more consecutive missing/unevaluable tumor assessments immediately before documented progression or death will be handled with the **hypothetical** strategy: DOR and PFS will be assessed based on tumor assessments had two consecutive tumor assessments not been missed immediately before documented progression or death.
- Population-level summary will include the Kaplan Meier estimate of DOR and PFS and corresponding CIs at specified time points. Confidence intervals for KM estimates will be estimated for each treatment group using the Kaplan Meier method and log-log approach based on a normal approximation following the Greenwood's formula. The quantiles of DOR and PFS and corresponding CI from Kaplan Meier method will also be provided, CI will be constructed using a log-log transformation of the survival function and the methods of Brookmeyer and Crowley. In the absence of disease progression or death before the cut-off date, DOR and PFS will be censored as indicated in Table 4. Quantiles will also be provided.

**Table 4 - Censoring rules for DOR and PFS**

| Situation | Date of progression or censoring | Outcome | Category |
|---|---|---|---|
| No baseline tumor assessments[a] | Date of first treatment intake | Censored | No baseline tumor assessments |
| No evaluable[b] post-baseline tumor assessments[a] | Date of first treatment intake | Censored | No evaluable post-baseline tumor assessments |
| Progression documented at or between scheduled visits | Date of the first tumor assessment documenting progression | Event | Documented progression |
| New anticancer treatment before documented progression | Date of the last evaluable tumor assessment before new treatment | Censored | New anticancer treatment |
| Death prior to the first planned post-baseline tumor assessment[a] | Date of death | Event | Death |
| Death at or between scheduled visits | Date of death | Event | Death |
| Death or documented progression immediately after two[c] or more missed or non-evaluable tumor assessments | Date of the last evaluable tumor assessment documenting no progression | Censored | Death or progression after two or more missed/unevaluable tumor assessments |
| Alive and no documented progression | Date of the last evaluable tumor assessment | Censored | Alive without documented progression |

*a* Not applicable for DOR.
*b* Evaluable TA means an evaluation different from non-evaluable.
*c* Two consecutive tumor assessments are considered as missed/non-evaluable if the duration between two consecutive tumor assessments done (non-missing) and evaluable is strictly longer than 20 weeks.

The clinical benefit rate will be summarized using the same estimand as for the primary endpoint.

### 3.3.2 Supportive secondary endpoint(s)

Not applicable.

## 3.4 TERTIARY/EXPLORATORY ENDPOINT(S) ANALYSIS

### 3.4.1 Definition of endpoint(s)

[redacted]

[redacted]

[redacted]

[redacted]

### 3.4.2 Main analytical approach

[redacted]

[redacted]

## 3.5 MULTIPLICITY ISSUES

No formal testing will be performed. Therefore, no multiplicity issues need to be addressed.

## 3.6 SAFETY ANALYSES

The analysis of the safety variables will be descriptive, and no testing is planned.

### 3.6.1 Extent of exposure

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

#### *3.6.1.1 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 interventions is administered.
- Duration of IMP exposure (in months) is defined as: (Last day of exposure – first day of exposure +1)/30.4375.
- The first day of exposure is defined as the first administration date with non-zero dose for at least one of the IMP (SAR444245 or cetuximab or pembrolizumab).

  The last day of exposure is the day before the theoretical date of the next administration (after the last administration), defined as the maximum between:

  - The last administration date + 20 days for SAR444245,
  - The last administration date + 6 days for cetuximab.
  - The last administration date + 20 days for pembrolizumab.

The total number of cycles started, and cumulative total number of cycles started by participants will be summarized by category. 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 – theoretical duration of a cycle – start date of the previous cycle is ≥4 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 at 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 more than 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 more than 7 days.

#### *3.6.1.2 SAR444245 exposure*

The dose information will be assessed by the following:

- Duration of SAR444245 exposure (in months) is defined by (date of last administration of SAR444245 + 21 – date of first administration of SAR444245)/30.4375.
- Total number of cycles started for SAR444245 per participant
- Actual dose (µg/kg)
- Cumulative dose (µg/kg): the cumulative dose is the sum of all actual doses of SAR444245, given from first to last administration
- Actual dose intensity (ADI in µg/kg/week): defined as the cumulative dose divided by the duration of SAR444245 exposure (in weeks)
- Planned dose intensity (PDI in µg/kg/week): corresponds to the planned dose at C1D1 and divided by the theoretical cycle duration expressed in weeks (ie, 3 weeks)
- Relative dose intensity (RDI, in %): $100 \times \frac{\text{ADI (µg/kg/week)}}{\text{PDI (µg/kg/week)}}$

The total number of cycles started; number of cycles started by participant will be summarized by category. Duration of SAR444245 exposure, cumulative dose, ADI and RDI will be summarized quantitatively and RDI will also be summarized by category if relevant.

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 SAR444245 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 - SAR444245 dose reduction criteria**

| Actual dose level | Dose level interval |
|---|---|
| 8 µg/kg | [redacted] |
| 16 µg/kg | |
| 24 µg/kg | |

- Dose omission is defined as a dose not administered at the scheduled visit.
- Dose interruption: A dose will be considered as interrupted if SAR444245 administration is stopped during an infusion regardless of whether it is restarted or not.

Dose modifications and dose interruptions will be analyzed by participant and dose 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 reduction
    - Number (%) of participants with at least 1 dose omission
  - Number (%) of participants with at least 1 dose interruption
    - Number (%) of participants with at least 1 dose interrupted and restarted
    - Number (%) of participants with at least 1 dose interrupted and not restarted
  - Number (%) of participants with at least 2 dose interruptions
- **Dose** (number of doses started will be used as denominator)
  - Number (%) of doses
  - Number (%) of dose interruptions
  - Number (%) of doses interrupted and re-started
  - Number (%) of doses interrupted and not re-started
  - Number (%) of doses interrupted more than once,
  - Number (%) of doses interrupted at 1st dose, 2nd dose, subsequent doses,
  - Time from dose start to first interruption in minutes summarized as a continuous variable and by category.

#### *3.6.1.3 Cetuximab exposure*

The dose information will be assessed by the following:

- Total number of cycles started for cetuximab per participant
- Duration of cetuximab (in months) is defined by (date of last administration of cetuximab + 7 – date of first administration of cetuximab)/30.4375.
- Actual dose (mg/m²)
- Cumulative dose (mg/m²): the cumulative dose is the sum of all actual doses of cetuximab, given from first to last administration
- Actual dose intensity (ADI in mg/m²/week): defined as the cumulative dose divided by the duration of cetuximab exposure (in weeks)
- Planned dose intensity (PDI in mg/m²/week): corresponds to the sum of planned dose started and divided by duration of cetuximab exposure (in weeks)
- 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; number of cycles started by participant will be summarized by category. Duration of cetuximab exposure, cumulative dose, ADI and RDI will be summarized quantitatively. Relative dose intensity will also be summarized by category if relevant.

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

- Dose reduction: The first and second administration will not be counted as a dose reduction. For the third and subsequent cetuximab 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 6 - Cetuximab dose reduction criteria**

| Actual dose level | Dose level interval |
|---|---|
| 150 mg/m² | >0 and ≤175 mg/m² |
| 200 mg/m² | >175 mg/m² and ≤225 mg/m² |
| 400 mg/m² then 250 mg/m² | >225 mg/m² |

- Dose omission is defined as a dose not administered at the scheduled visit.
- Dose interruption: A dose will be considered as interrupted if cetuximab administration is stopped during an infusion regardless of whether it is restarted or not.

Dose modifications and dose interruptions will be analyzed by participant 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 reduction
    - Number (%) of participants with at least 1 dose omission
  - Number (%) of participants with a least 1 dose interruption
    - Number (%) of participants with at least 1 dose interrupted and restarted
    - Number (%) of participants with at least 1 dose interrupted and not restarted
  - Number (%) of participants with at least 2 dose interruptions.

#### *3.6.1.4 Pembrolizumab exposure*

The dose information will be assessed by the following:

- Total number of cycles started for pembrolizumab per participant
- Duration of pembrolizumab (in months) is defined by (date of last administration of cetuximab + 21 – date of first administration of pembrolizumab)/30.4375.
- Actual dose (mg)
- Cumulative dose (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 at C1D1 divided by the theoretical cycle duration expressed in weeks (ie, 3 weeks)
- Relative dose intensity (RDI, in %): $100 \times \frac{\text{ADI (mg/week)}}{\text{PDI (mg/week)}}$

The total number of cycles started; number of cycles started by participant will be summarized by category. Duration of pembrolizumab exposure, cumulative dose, ADI and RDI will be summarized quantitatively. RDI will also be summarized by category.

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

- Dose omission is defined as a dose not administered at the scheduled visit.
- Dose interruption: A dose will be considered as interrupted if pembrolizumab administration is stopped during an infusion regardless of whether it is restarted or not.

Dose modifications and dose interruptions will be analyzed by participant as follows:

- **Participant** (number of participants treated will be used as denominator)
  - Number (%) of participants with at least 1 dose omission
  - Number (%) of participants with a least 1 dose interruption
  - Number (%) of participants with at least 1 dose interrupted and restarted
  - Number (%) of participants with at least 1 dose interrupted and not restarted
  - Number (%) of participants with at least 2 dose interruptions.

### 3.6.2 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. Cytokine Release Syndrome (CRS) and Immune effector cell associated neurotoxicity syndrome (ICANS) will be graded using ASTCT Consensus grading.

The AEs will be analyzed in the following 3 categories:

- Pre-treatment AEs: AEs occurring during the pre-treatment period.
- Treatment-emergent adverse events (TEAEs): AEs that developed, worsened (according to the Investigator's opinion) 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 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. 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 6.

**Table 6 - 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] |
| PT | By decreasing frequency of PTs[a] |

*a* Sorting will be based on the AE incidence.
*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 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
- Any treatment-emergent SAE
- Treatment related TEAEs
- Treatment related TEAE of Grade ≥3
- Serious treatment related TEAEs
- Grade 5 TEAE (any TEAE with a fatal outcome during the treatment-emergent period)
- Any TEAE leading to permanent full intervention discontinuation
- Any TEAE leading to permanent partial intervention discontinuation (discontinuation of each individual drug)

The AE summaries of Table 7 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 7 - Analyses of adverse events**

| Type of AE | MedDRA levels |
|---|---|
| All TEAE | Primary SOC, HLGT, HLT and PT<br>Primary SOC and PT |
| TEAE related to IMP (overall) as per Investigator's judgment | Primary SOC and PT |
| Treatment emergent SAE | Primary SOC and PT |
| Treatment emergent SAE related to IMP (overall) as per Investigator's judgment | Primary SOC and PT |
| TEAE leading to permanent full intervention discontinuation | Primary SOC and PT |
| TEAE leading to permanent partial intervention discontinuation (for each individual drug) | 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 |
| AE leading to death[a] | Primary SOC and PT |
| - In context of disease progression[b] | |
| - In context other than disease progression[c] | |
| Pre-treatment AE | Primary SOC and PT |
| Post-treatment AE | Primary SOC and PT |
| TEAE leading to dose interruption | Primary SOC and PT |
| TEAE leading to dose modification (including dose reduction, dose omission and dose delay) | Primary SOC and PT |

*a* Death as an outcome of the AE as reported by the Investigator in the AE page
*b* Death within 30 days from last IMP administration and the cause of death is disease progression
*c* Death within 30 days from last IMP administration and for whom cause of death is not disease progression or the death occurred more than 30 days from last IMP administration and the cause of death is AE

## Analysis of deaths

In addition to the analyses of deaths included in Table 6, the number (%) of participants in the following categories will be provided:

- Deaths during the treatment-emergent and post-treatment periods by main reason for death
- 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).

**Analysis of adverse events of special interest (AESIs)**

Number (%) of participants experiencing at least one adverse event of special interest will be provided, by system organ class (SOC) and preferred term (PT). The selection will be made using the electronic case report form (eCRF) specific **AESI** tick box. Tables will be sorted as indicated in Table 6.

In addition, the following analyses will be done for infusion reactions categories (ie, infusion related reactions [IRRs], cytokine release syndrome [CRS], flu-like symptoms [FLS] and anaphylaxis):

- Description of the infusion reactions by predefined grouping and other reported PT
- Worst grade
- Action taken for each IMP
- Corrective treatment given (Yes, No)
- Number (%) of patients with only 1 episode, ≥2, ≥3, ≥4 and ≥5 episodes
- Onset of first episodes of infusion reactions (at the first infusion and subsequent infusions)
- Number (%) of patients with infusion reactions (any episodes) at the first and subsequent infusions
- Number (%) of patients with at least one infusion with two episodes of infusion reactions
- Total number of infusion reaction episodes
- Time to onset from infusion (by category: infusion day/1 day after infusion/2 to 3 days from infusion/More than 3 days from infusion when applicable)
- Duration of infusion reactions (in days) (by category 1 day/2 to 3 days/more than 3 days/not recovered)
- Number (%) of patients with infusion reactions symptoms (as reported by Investigator) by SOC and PT.

### 3.6.3 Additional safety assessments

#### *3.6.3.1 Laboratory variables, vital signs*

The following laboratory variables and vital signs variables will be analyzed. They will be converted into standard international units.

- Hematology:
  - Red blood cells and platelets: hemoglobin, hematocrit, platelet count
  - White blood cells: leukocytes, neutrophils, lymphocytes, monocytes, basophils, eosinophils

- Clinical chemistry:
  - Metabolism: glucose, albumin, lipase, amylase
  - Electrolytes: sodium, potassium, chloride, calcium corrected, bicarbonate, magnesium

    Calcium Corrected (mmol/L) = Total calcium (mmol/L) + 0.8 * 0.25 * [4 – Serum albumin (g/L) * 0.1]
  - Renal function: creatinine, estimated glomerular filtration rate (eGFR), blood urea nitrogen.
  - Liver function: alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, lactate dehydrogenase, bilirubin
- Vital signs: heart rate, systolic and diastolic blood pressure, respiratory rate, temperature, Eastern Cooperative Oncology Group (ECOG) Performance status

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 upper limit of quantification (ULOQ) value.

For hematological parameters and some selected biochemistry parameters, Sanofi sponsor generic ranges (lower limit of normal [LLN], upper limit of normal [ULN]) are defined and will be used for grading (see list of parameters in Section 5.4). For other biochemistry parameters, grading will be derived using local laboratory normal ranges.

**Quantitative analyses**

When relevant, for laboratory variables and vital signs above, descriptive statistics for results and changes from baseline will be provided for the last value and the worst value (minimum and/or maximum value depending on the parameter) during the on-treatment period. These analyses will be performed using local measurements for laboratory variables.

**Analyses according to potentially clinically significant abnormality (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 eGFR, blood urea nitrogen, hematocrit, monocytes, basophils, and chloride, 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 and vital signs 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.

## 3.7 OTHER ANALYSES

### 3.7.1 Other variables and/or parameters

#### *3.7.1.1 PK analyses*

No PK parameters will be assessed, as only sparse sampling for pharmacodynamic concentrations of SAR444245 is implemented in the study.

**Table 8 - List of PK concentrations and definitions**

| PK concentrations | Definition | Sparse PK SAR444245 | Sparse PK Cetuximab |
|---|---|---|---|
| $C_{through}$ | Concentration observed just before intervention administration during repeated dosing | | X |
| $C_{EOI}$ | Concentration at end of infusion | X | X |
| $C_{D2}$ | Concentration taken any time at day 2 after previous administration | X | |

Applicable concentrations for SAR444245 ($C_{EOI}$, $C_{D2}$) and for Cetuximab ($C_{through}$, $C_{EOI}$) will be described on the PK population for each planned visit using the following descriptive statistics: mean, geometric mean, median, standard deviation, coefficient of variation, minimum, and maximum. These analyses will be performed by specific subgroups (eg, gender, body mass index [BMI], age) if appropriate.

All concentration values below the lower limit of quantitation (LLOQ) will be treated as zero in all summary statistics. Geometric mean will not be computed in case at least one concentration is below LLOQ.

#### *3.7.1.2 Immunogenicity analyses*

Participant's ADA status, response variable and kinetics of ADA responses (see definitions below) will be summarized on the ADA population.

Kinetics of ADA responses will be described for participants with treatment-induced ADA and for participants with treatment-boosted ADA, separately. Time to ADA onset and duration of ADA will be described with minimum, Q1, median, Q3 and maximum statistics.

Peak titer will be described with minimum, Q1, median, Q3 and maximum statistics for participants with treatment-induced ADA and for participants with treatment-boosted ADA, separately.

ADAs against SAR444245 (negative, positive, inconclusive) and corresponding titers, ADAs directed against PEG moiety of SAR444245 status (negative, positive) and ADAs cross-reacting with endogenous IL-2 status (negative, positive) will also be described overtime using descriptive statistics.

ADAs directed against PEG moiety of SAR444245 status and ADAs cross-reacting with endogenous IL-2 status will only be determined if ADAs against SAR444245 status is positive.

The impact of positive immune response on efficacy, PK and safety variables may be further explored, depending on ADA incidence.

***Participant's ADA status against SAR444245***

- Participants with **pre-existing ADA**s correspond to participants with ADAs present in samples drawn before first administration of intervention. Participants with missing ADA sample at baseline will be considered as without pre-existing ADA.
- Participants with **treatment-emergent ADA** correspond to participants with at least one treatment-induced/boosted ADA.
    - Participants with **treatment-induced ADA**s correspond to participants with ADAs that developed during the treatment-emergent (TE) period and without pre-existing ADA (including participants without pre-treatment samples).
    - Participants with **treatment-boosted ADA**s correspond to participants with pre-existing ADAs that are boosted during the TE period to a significant higher titer than the baseline. A 2-fold serial dilution schema is used during titration, so at least a 4-fold increase will be considered as significant.
- Participants with **unclassified ADA** correspond to participants with pre-existing ADAs that cannot be classified as treatment-boosted ADA because of missing titer(s) (ie, a positive ADA sample during the TE period in a participant with pre-existing ADA but with missing titer at this sample or at baseline).
- Participants **without treatment-emergent ADA** correspond to participants without treatment-induced/boosted ADA and without any inconclusive sample nor unclassified ADA during the TE period.
- Participants **with inconclusive ADA** are defined as participants which cannot irrefutably be classified as with or without treatment-emergent ADA.

***Kinetics of ADA response***

Kinetics of ADA response will be derived for participants with treatment-induced/boosted ADA considering ADA samples collected during the TE period and post-treatment period.

- **Time to onset of ADA response** is defined as the time period between the first IMP administration and the first treatment-induced/boosted ADA.
- **Duration of ADA response** is defined as the time between the first treatment-induced/ boosted ADA and the last treatment-induced/boosted ADA, irrespective of negative samples or positive samples not reaching the boosted threshold in-between. ADA duration will be summarized only for participants with persistent ADA response.
  - A positive sample (boosted positive sample for participants with pre-existing ADA) occurring after the TE period will be considered as treatment-induced/boosted ADA if a previous treatment-induced/boosted ADA occurred during the TE period and less than 16 weeks before this sample.
- **Persistent ADA response** is defined by treatment-induced/boosted ADA with a duration of ADA response of at least 16 weeks.
- **Transient ADA response** is defined by treatment-induced/boosted ADA with a duration of ADA response of less than 16 weeks and the last sample of the TE period is not treatment-induced/boosted.
- **Indeterminate ADA response** is defined by treatment-induced/boosted ADA that are neither persistent nor transient.

***ADA response variable:***

- **ADA incidence** is defined as the proportion of participants found to have seroconverted (treatment-induced ADAs) or boosted their pre-existing ADA response (treatment-boosted ADAs) at any time point during the TE period.
- **Incidence of ADAs directed against PEG moiety of SAR444245** is defined as the proportion of participants with ADAs directed against PEG moiety of SAR444245 during the TE period among evaluable participants. Participants from ADA population are evaluable for ADAs directed against PEG moiety except if ADAs directed against PEG moiety status is not determined on an ADA against SAR444245 positive sample.
- **Incidence of ADAs cross-reacting with endogenous IL-2** is defined as the proportion of participants with ADAs directed against endogenous IL-2 during the TE period among evaluable participants. Participants from ADA population are evaluable for ADAs directed against endogenous IL-2 except if their status is not determined on an ADA against SAR444245 positive sample.

#### *3.7.1.3 Biomarker analyses*

### 3.7.2 Subgroup analyses

Analyses will be performed on the primary endpoint across the following subgroups (categories with fewer than 5 participants may be combined with other categories):

**Table 9 - Subgroup analyses**

| | A1 | A2 | B1 | B2 |
|---|---|---|---|---|
| Number of prior systemic therapy regimens (0 versus 1-2) | | | Yes | Yes |
| LDH laboratory results at baseline (normal versus abnormal) | Yes | Yes | Yes | Yes |
| Histopathology subtype at baseline (Squamous cell carcinoma or other) | Yes | Yes | Yes | Yes |
| Location at baseline (Hypopharynx, Larynx, Oral Cavity, Oropharynx, Tonsil, or other locations) | Yes | Yes | Yes | Yes |
| PD-L1 status at baseline (<1% versus ≥1%) | Yes | Yes | | |

The ORR will be provided, as well as the corresponding 90% CI, for each subgroup, using the same method as applied to the primary analysis.

## 3.8 INTERIM ANALYSES

No formal interim analyses are planned. However, at the end of the safety run-in part (cohort A2 only), the occurrence of DLT and other safety data will be reviewed by Study Board (SB) to confirm safe dose for further continuation.

After the dose is confirmed by the SB, the cumulative safety data for each study intervention across cohorts will be reviewed periodically by the DMC. The enrollment will not be paused or stopped during the safety monitoring unless severe safety concern arises. DMC will review safety data periodically. Ad hoc DMC meetings may also be held if a significant safety issue or an issue deemed important for discussion arises on this or other SAR444245 studies. The DMC procedures will be detailed in the DMC charter and approved by the DMC members.

In addition, for each cohort, in order to support project strategic planning and design of future studies, informal interim analysis(es) may be conducted during the dose expansion part of the study, eg, after 20 participants have undergone at least 2 post-baseline tumor assessments or have discontinued the study intervention, whichever is earlier.

The cohort cut-off for the primary ORR endpoint analysis corresponds to approximately 9 months from the date of the last participant's first infusion (to document that last participant response is maintained for 6 months).

For each cohort, the cut-off date for the final analysis (ie, analysis of secondary objectives and update of primary objective) will be 3 years from cohort last patient-in (LPI).

## 3.9 CHANGES TO PROTOCOL-PLANNED ANALYSES

This section summarizes major statistical changes in the protocol amendment(s).

**Major statistical changes in protocol amendment(s)**

| Amendment Number | Approval Date | Changes | Rationale |
|---|---|---|---|
| 3 | 22/12/2021 | 1.1 Synopsis, 3 Objectives and Endpoints: Table 2, 9.4.3.1 Time to response, and 9.4.3.2 Duration of response Definitions of Time to response and Duration of response have been revised as follows:<br>• Time to response (TTR) defined as the time from the first administration of investigational medicinal product (IMP) to the first tumor assessment at which the overall response was recorded as PR or CR that is subsequently confirmed and determined by investigator per RECIST 1.1.<br>• Duration of response (DoR), defined as the time from first tumor assessment at which the overall response was recorded as PR or CR that is subsequently confirmed until documented progressive disease (PD) determined by investigator per RECIST 1.1 or death from any cause, whichever occurs first. | For clarification |

| Amendment Number | Approval Date | Changes | Rationale |
|---|---|---|---|
| 3 | 22/12/2021 | 1.1 Synopsis and 9.4.3.5 Adverse Events<br>Analyses of adverse events (AEs) related to specific IMP have been removed as treatment-related treatment-emergent adverse events (TEAEs) will be analyzed overall, regardless of the drug. | To assess treatment-related AE of the regimen as whole (SAR444245 with other anticancer therapies) |
| 3 | 22/12/2021 | 9.3 Populations for Analyses<br>The efficacy population definition was revised to "All participants from the exposed population with at least one evaluable post-baseline tumor assessment or who permanently discontinued study treatment". | To characterize the efficacy excluding participants newly enrolled |
| 3 | 22/12/2021 | 9.4.3.6 Clinical laboratory evaluations and 9.4.5 Other safety analyse(s)<br>Descriptive statistics for laboratory variables and vital signs will be performed only when relevant. The following text was deleted: "These analyses will be performed using local measurements for laboratory variables". | These analyses will be done as needed following analyses of abnormalities according to NCI-CTCAE grade |
| 3 | 22/12/2021 | 9.4.5 Other safety analyse(s)<br>"ECG" was removed from quantitative analyses. | ECG data are not collected systematically during the treatment period |
| 3 | 22/12/2021 | 10.9 Appendix 9: Response evaluation criteria in solid tumors (RECIST) 1.1<br>"Or progressive disease" has been removed from the sentence "Confirmatory scans should also be obtained at least 4 weeks following initial documentation of objective response or progressive disease". | To correct a typographical error |

# 4 SAMPLE SIZE DETERMINATION

Overall, in the core phase, the plan is to treat approximately 40 participants per cohort.

The following table lists estimated ORR and the corresponding 90% exact CIs by number of responders from a sample size of 40 participants exposed in each cohort in core phase.

**Table 10 - Estimated objective response rate (ORR) and 90% CI for core phase**

| Number of responders (N=40) | Objective Response Rate in % | 90% Clopper-Pearson CI |
|---|---|---|
| 6 | 15.0% | (6.7% - 27.5%) |
| 7 | 17.5% | (8.5% - 30.4%) |
| 8 | 20.0% | (10.4% - 33.2%) |
| 9 | 22.5% | (12.3% - 36.0%) |
| 10 | 25.0% | (14.2% -38.7 %) |
| 11 | 27.5% | (16.3% -41.4 %) |
| 13 | 32.5% | (20.4% -46.6%) |
| 15 | 37.5% | (24.7% - 51.7%) |
| 17 | 42.5% | (29.2% - 56.7%) |
| 19 | 47.5% | (33.8% -61.5 %) |
| 24 | 60.0% | (45.8% -73.1 %) |

With a sample size of 40 study participants in each cohort in the core phase, the probability of observing 1 or more instances of a specific AE with a true incidence rate of 1%, 2%, or 5% is 33.1%, 55.4%, or 87.1%, respectively. This provides reasonable assurance that events occurring at ≥5% frequency can be identified in this study.

# 5 SUPPORTING DOCUMENTATION

## 5.1 APPENDIX 1: LIST OF ABBREVIATIONS

ADA: Anti-Drug Antibodies
ADI: actual dose intensity
AE: adverse event
AESI: adverse event of special interest
BMI: body mass index
BOR: best overall response
CI: confidence interval
COVID-19: Coronavirus Disease 2019
CPS: combined positive score
CR: complete response
[redacted]
CRS: cytokine release syndrom
[redacted]
DLT: dose limiting toxicities
DMC: data monitoring committee
DNA: deoxyribonucleic acid
DoR: duration of response
ECG: electrocardiogram
ECOG: Estern Cooperative Oncology Group
eGFR: estimated Glomerular Filtration Rate
EOI: end of infusion
HLGT: high-level group term
HLT: high-level term
HNSCC: head and neck squamous cell carcinoma
[redacted]
IE: intercurrent event
IMP: investigated medicinal product
[redacted]
ITT: intent-to-treat
KM: Kaplan Meier
LLN: lower limit of normal
LLOQ: lower limit of quantification
LLT: lower level term
LPI: last patient in
MedDRA: Medical Directory for Regulatory Activities
NAT: new anticancer therapy
NCI-CTCAE: national cancer institute common terminology for adverse events
OR: objective response
ORR: objective response rate
[redacted]

| | |
|---|---|
| PCSA: | potentially clinically significant abnormality |
| PD: | progressive disease, progressive disease |
| PD1: | programmed cell death protein |
| PDI: | planned dose intensity |
| PD-L1: | programmed cell death-ligand 1 |
| PFS: | progression-free survival |
| PK: | pharmacokinetic |
| PR: | partial response |
| PT: | preferred term |
| R/M: | recurrent/metastatic |
| RDI: | relative dose intensity |
| RECIST: | response evaluation criteria in solid tumor |
| RP2D: | recommended Phase II dose |
| SAE: | serious adverse event |
| SAP: | statistical analysis plan |
| SB: | study board |
| SD: | stable disease |
| SD: | standard deviation |
| SOC: | system organ class |
| TA: | tumor assessment |
| TE: | treatment emergent |
| TEAE: | treatment-emergent adverse event |
| [redacted] | |
| TTR: | time to response |
| ULN: | upper limit of normal |

## 5.2 APPENDIX 2: PARTICIPANT DISPOSITIONS

The number (%) of participants included in each of the analysis populations listed in Table 3 will be summarized. Reasons for exclusion from the population without trial impact (disruption) due to COVID-19 will be summarized.

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 intervention discontinuation, the following definitions will be used:

- Permanent **partial** intervention discontinuation is defined as the discontinuation of one of the study drugs (SAR444245 or cetuximab and/or pembrolizumab) but the other 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 exposed participants
- Exposed participants
- Participants still on study intervention
- Participants who did not complete the study treatment period as per protocol and main reason for permanent full intervention discontinuation.
- Participants who did not complete the study treatment period as per protocol for SAR444245 and main reason for permanent partial intervention discontinuation (discontinuation of SAR444245).
- Participants who completed the study period as per protocol.
- Participants who did not complete the study period as per protocol and main reason for study discontinuation.

Reasons for permanent study intervention and study discontinuation "adverse event" and "other reasons" will be split as related versus not related to COVID-19, if applicable.

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

Protocol deviations

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

## 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 exposed population.

Demographic and baseline characteristics

- Age in years as quantitative variable and in categories (<65, 65 to <75, ≥75)
- Gender (Male, Female)
- Race
  - White

  - Black/Black or African American
  - Asian
  - Native Hawaiian or Other Pacific Islander
  - American Indian or Alaska Native
  - Japanese
  - Not reported
  - Unknown
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not reported, Unknown)
- BMI
- Eastern Cooperative Oncology Group (ECOG) performance status (PS)

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 smoking status. 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 characteristics at diagnosis includes:

- Time from initial diagnosis of cancer to first study treatment infusion (in years)
- Histology type
- Location
- Stage of the disease
- T staging
- N staging
- M staging

Specific disease status at study entry includes:

- Extent of the disease
- Number of organ(s) involved

Type of organ(s) involved

***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 used 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(s) from the first administration of IMP to the last IMP intake + 30 days.
- Post-treatment medications are those the participant took in the period after the end of the concomitant medications period.
- 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 taken prior or concomitantly or post, it will be considered as prior, concomitant, and post-treatment medication.

The prior and concomitant medications will be summarized for the exposed population, by anatomic and therapeutic level. The summaries will be sorted by decreasing frequency of anatomic category (ATC). In case of equal frequency, alphabetical order will be used. Participants will be counted once in each ATC category (anatomic or therapeutic) linked to the medication.

***Anticancer therapies***

Prior anticancer therapies will be described, including several characteristics such as:

- Therapy type
- Intent of prior anti-cancer therapy
- Number of prior regimens
- Time from last relapse/progression to first IMP administration (months)
- Number of prior lines in advanced settings
- Type of prior anti-cancer therapy
- Intent of the last prior anti-cancer therapy
- Prior radiation therapy
- Prior surgery related to skin
- Reason for discontinuation of the last regimen
- Best response to the last prior regimen
- Time to progression of the last prior regimen (months)
- Duration of last regimen (months)

Subsequent therapies after discontinuation of intervention will be summarized based on WHO-DD coding.

***Pre-medications***

Number (%) of patients with the following pre-medications will be provided. Number (%) of patients with pre-medications will be provided by infusions at Cycle 1, Cycle 2, Cycle 3 and Cycle 4. Number (%) of infusions with pre-medications will be provided overall for subsequent cycles.

- Acetaminophen (paracetamol)
- Diphenhydramine (or equivalent eg, cetirizine, promethazine, dexchlorpheniramine, according to local approval and availability)
- Ondansetron (or equivalent eg, granisetron, dolasetron, tropisetron, palonosetron)
- Others

## 5.4 APPENDIX 4: SANOFI SPONSOR RANGES

| Test | Gender | Unit | Lower/upper limit of normal |
|---|---|---|---|
| Basophils | | 10^9/L | 0 – 0.15 |
| Eosinophils | | 10^9/L | 0 – 0.4 |
| Erythrocytes | Male | 10^12/L | 4.5 – 5.9 |
| Erythrocytes | Female | 10^12/L | 4 – 5.2 |
| Hemoglobin | Male | g/L | 135 – 175 |
| Hemoglobin | Female | g/L | 120 – 160 |
| Hematocrit | Male | v/v | 0.41 – 0.53 |
| Hematocrit | Female | v/v | 0.36 – 0.46 |
| Leukocytes | | 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 | | 10^9/L | 150 – 350 |
| Albumin | | g/L | 35 – 55 |
| Urea Nitrogen | | mmol/L | 3.6 – 7.1 |
| Chloride | | mmol/L | 80 – 115 |
| Glucose | | mmol/L | 3.900001 – 6.999999 |
| Bicarbonate (HCO3) | | mmol/L | 22 – 29 |
| Potassium | | mmol/L | 3.5 – 5 |
| Magnesium | | mmol/L | 0.8 – 1.2 |
| Sodium | | mmol/L | 136 – 145 |
| Phosphate | | mmol/L | 1 – 1.4 |
| Protein | | g/L | 55 – 80 |
| Urea | | mmol/L | 3.6 – 7.1 |
| INR | | Ratio | 0.8 – 1.2 |
| Calcium corrected | | mmol/L | 2.2 – 2.6 |

## 5.5 APPENDIX 5: DATA HANDLING CONVENTIONS

### Unscheduled visits

Unscheduled visit measurements of laboratory data, vital signs and ADA will be used for computation of baseline, the worst on-treatment value, analysis according to PCSAs/NCI grade, and the shift summaries for safety.

# 6 REFERENCES

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