STATISTICAL ANALYSIS PLAN

Protocol title:	**A Phase 1/2 non-randomized, open-label, multi-cohort, multi-center study assessing the clinical benefit of SAR444245 (THOR- 707) combined with cemiplimab for the treatment of participants with advanced unresectable or metastatic skin cancers**
Protocol number:	**ACT16845**
Compound number (INN/Trademark):	**SAR444245 (Not applicable)**
Study phase:	**Phase 1/2**
Short Title:	**A study of SAR444245 combined with cemiplimab for the treatment of participants with various advanced skin cancers Pegathor Skin 201**
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VERSION HISTORY

This statistical analysis plan (SAP) for Study ACT16845 is the first version and is based on the Amended protocol 04 dated 20-Oct-2021. This section summarizes the major changes to the statistical analysis features in the SAP.

The first participant was enrolled on 13-Sep-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 04

1 INTRODUCTION

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

1.1 STUDY DESIGN

This is a Phase 1/2, multi-cohort, un-controlled, non-randomized, open-label, multi-center study assessing the antitumor activity and safety of SAR444245 combined with the immune checkpoint inhibitor (ICI) cemiplimab in ICI-naïve participants with advanced, unresectable, or metastatic skin cancers.

After a screening period of up to 28 days, participants will receive treatment in one of the two independent cohorts in parallel depending on the type of skin cancer:

- **Cohort A** will include approximately 40 participants with previously untreated **locally advanced, unresectable or metastatic melanoma,** and will assess the investigational combination regimen as first-line (1L) therapy.
- **Cohort B** will include approximately 40 participants with ICI-naïve **metastatic cutaneous squamous cell carcinoma (CSCC) or locally advanced CSCC** who are not candidates for curative surgery or curative radiation and who have received no more than 2 prior lines of systemic therapy.

The study will start with a dose escalation to determine the recommended Phase 2 dose (RP2D) of SAR444245 when combined with cemiplimab. Dose escalation will proceed using Modified Toxicity Probability Interval Design (mTPI-2 design, Guo et al 2017 [1]). The starting dose will be 16 µg/kg Q3W (DL1) with a possibility to de-escalate to 8 µg/kg Q3W (DL -1) or escalate to 24 µg/kg Q3W (DL2) based on the occurrence of dose limiting toxicity (DLT) and overall assessment of safety. The plan is to treat a minimum number of 3 DLT evaluable participants at each dose-cohort and a minimum of 6 DLT-evaluable participants treated at RP2D will be needed before starting the dose expansion. During the dose escalation, decision for next dose level (de-escalate, stay, escalate) will occur after the last patient has completed the DLT observation period (first 21 days) for the previous dose level. The Study Board (SB) will review DLT and overall safety data for these participants and will make the next dose recommendation.

The determination of RP2D will be made by the SB after a minimum of 6 DLT-evaluable participants have been treated at the selected dose. Participants enrolled in the dose escalation and treated at the RP2D will be included in the total number of participants.

1.2 OBJECTIVES AND ENDPOINTS

Table 1 - Objectives and endpoints

Objectives	Endpoints
Primary	
• To determine the antitumor activity of SAR444245 in combination with cemiplimab.	• **Cohort A** (melanoma): Objective response rate (ORR) defined as the 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. • **Cohort B** (CSCC): ORR defined as the proportion of participants who have a confirmed CR or PR determined by Investigator per RECIST 1.1, or modified WHO criteria for medical photographs of external skin lesions, or composite criteria.
Secondary	
• To determine the recommended Phase 2 dose (RP2D) and to assess safety profile of SAR444245 when combined with cemiplimab.	• Incidence of treatment-emergent adverse event (TEAEs), dose limiting toxicities (DLTs), 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 gradings.
• To assess other indicators of antitumor activity.	• Complete Response rate (CRR) defined as the proportion of participants who have a confirmed CR determined by Investigator per RECIST 1.1 for melanoma participants and when applicable for CSCC participants (CR in localized unresectable CSCC is exploratory). • Time to CR 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 CR that is subsequently confirmed and determined by Investigator per RECIST 1.1 for melanoma participants and when applicable for CSCC participants. • Time to Response (TTR) 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 and determined by Investigator per RECIST1.1 or modified WHO criteria or composite criteria, whichever relevant. • Duration of Response (DOR), defined as the time from first tumor assessment at which the overall response was recorded as CR or PR that is subsequently confirmed until documented progressive disease (PD) determined by Investigator per RECIST 1.1 or modified WHO criteria for medical photographs or composite criteria when relevant, or death from any cause, whichever occurs first.

Objectives	Endpoints
	• 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 or modified WHO criteria for medical photographs or composite criteria whichever relevant). • Progression Free Survival (PFS), defined as the time from the date of first IMP administration to the date of the first documented disease progression determined by Investigator per RECIST 1.1, or modified WHO criteria for medical photographs when relevant or death due to any cause, whichever occurs first.
• To assess the concentrations of SAR444245 when given in combination with cemiplimab. • To assess the immunogenicity of SAR444245. • To assess active concentrations of cemiplimab when given in combination with SAR444245.	• Concentration of SAR444245. • Incidence of anti-drug antibodies (ADAs) against SAR444245. • C_{trough} and $C_{end\_of\_Infusion}$ of cemiplimab.
Exploratory	
[redacted]	

Objectives	Endpoints
[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 cemiplimab				
Primary endpoint (estimand 1)	Objective Response (OR) (confirmed CR or PR)	Efficacy	• While not initiating new anti-cancer therapy (NAT) • 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 CI will be calculated using Clopper Pearson methods.
Secondary objective: To assess other indicators of antitumor activity of SAR444245 in combination with cemiplimab				
Secondary endpoint (Estimand 2)	DOR	Responders from efficacy population	• Had NAT not been initiated (hypothetical strategy) • Regardless of early IMP discontinuation (treatment policy strategy) • 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 confidence interval 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) • Regardless of early IMP discontinuation (treatment policy strategy) • 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 confidence interval 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 dose escalation and dose expansion parts. The participants included in the dose escalation 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 cemiplimab).
Population without trial impact (disruption) due to COVID-19	All exposed participants: • without any critical or major deviation related to COVID-19 • and who did not permanently discontinue treatment due to COVID-19 • 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 dose escalation 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 two IMPs (SAR444245 or cemiplimab). For participants enrolled but not treated, the baseline value is defined as the last available value before enrollment.

The treatment arm are defined as following:

- Planned arm: combination of treatments with SAR444245 dose level equal to the intended dose of SAR444245 entered in the eCRF at C1D1

Unless otherwise specified, analyses will be performed per planned arm, by cohort, by dose (if applicable) and overall (if applicable). Participants enrolled in the dose escalation part and treated at the RP2D will be included in the analyses of the expansion part.

All efficacy analyses will be performed on the efficacy population. Objective response rate, as well as all other response-related efficacy endpoints will be primarily derived using the local radiologist's/Investigator's assessment for both cohorts and the following criteria:

- For Cohort A (melanoma): RECIST 1.1
- For Cohort B (CSCC): RECIST 1.1 or modified WHO criteria for medical photographs of external skin lesions or composite criteria

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. CI will be used for descriptive purposes only, without inference.

The BOR is defined as the best overall response observed from the date of first IMP until disease progression, death, cut-off date or initiation of subsequent anti-cancer therapy, whichever occurs first.

- A PR or a CR must be confirmed on a second examination done at least 4 weeks apart, in order to confirm the tumor 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 cemiplimab.
- 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 confidence interval 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. 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 cemiplimab.
- 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 complete response rate is defined as the proportion of participants who have a confirmed CR.

The time to response 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 time to complete response is defined as the time from the first administration of IMP to the first tumor assessment at which the overall response was recorded as 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 complete response rate will be summarized using the same estimand as for the primary endpoint (Section 3.2.2).

The time to response and time to complete response will be assessed on the subgroup of participants who have achieved confirmed OR and confirmed CR, respectively, 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 cemiplimab.
- 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. CIs for KM estimates will be estimated 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.

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 EXPLORATORY ENDPOINT(S) ANALYSIS

3.4.1 Definition of endpoint(s)

[redacted]

3.4.2 Main analytical approach

[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 cemiplimab).

  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 + 20 days for cemiplimab.

The total number of cycles started and 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:

- Total number of cycles started per participant
- Duration of SAR444245 exposure (in months) is defined by (date of last administration of SAR444245 + 21 – date of first administration of SAR444245)/30.4375.

- 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 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 Cemiplimab exposure

The dose information will be assessed by the following:

- Total number of cycles started per participant.
- Duration of cemiplimab (in months) is defined by (date of last administration of cemiplimab + 21 – date of first administration of cemiplimab)/30.4375.
- Actual dose (mg).
- Cumulative dose (mg): the cumulative dose is the sum of all actual doses of cemiplimab, given from first to last administration.
- Actual dose intensity (ADI in mg/week): defined as the cumulative dose divided by the duration of cemiplimab 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 doses, total number of cycles started, number of cycles started by participant will be summarized by category. Duration of cemiplimab exposure, cumulative dose, ADI and RDI will be summarized quantitatively and by category if relevant.

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 cemiplimab 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 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.

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 (TEAE)s: AEs that developed, worsened (according to the Investigator's opinion) or became serious during the treatment-emergent period
- Post-treatment AEs: AEs that are reported 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 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

Type of AE	MedDRA levels
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)[a]	Primary SOC and PT
AE leading to death[a] • In context of disease progression[b] • In context other than disease progression[c]	Primary SOC and PT
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 cycle 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 SOC and PT. The selection will be made using the eCRF specific **AESI** tick box. Tables will be sorted as indicated in Table 6.

In addition, the following analyses will be done for infusion reaction category (selected by eCRF specific form) which are infusion related reactions (IRRs), cytokine release syndrome (CRS), flu-like symptoms (FLS) and anaphylaxis:

- Description of the infusion reaction category by predefined grouping and other reported PT.

- Worst grade.
- Action taken for each IMP.
- Corrective treatment given (Yes, No).
- Number (%) of participants with only 1 episode, ≥2, ≥3, ≥4 and ≥5 episodes.
- Onset of first episode of infusion reaction (at the first infusion and subsequent infusions).
- Number (%) of participants with infusion reactions (any episode) at the first and subsequent infusions.
- Number (%) of participants 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 reaction (in days) (by category 1 day/2 to 3 days/More than 3 days/not recovered).
- Number (%) of participants with infusion reactions symptoms (as reported by investigator) by SOC and PT.

3.6.3 Additional safety assessments

3.6.3.1 Laboratory variables and 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, 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, 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 ULOQ value.

For hematological parameters and some selected biochemistry parameters, Sanofi sponsor generic ranges (LLN, 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 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 and cemiplimab is implemented in the study.

Table 8 - List of PK concentrations and definitions

PK concentrations	Definition	Sparse PK SAR444245	Sparse PK cemiplimab
C_{trough}	Concentration observed just before intervention administration during repeated dosing	X	X
C_{EOI}	Concentration at end of infusion		X
C_{D2}	Concentration taken any time at Day 2 after previous administration	X	
C_{D3}	Concentration taken any time at Day 3 after previous administration	X	

Applicable concentrations for SAR444245 (C_{eoi}, C_{D2}, C_{D3}) and cemiplimab (C_{trough}, 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, 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 the status of ADAs against SAR444245 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

[redacted]

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

	CSCC	Melanoma
HPV status at baseline (positive versus negative)	Yes	
Number of prior systemic therapy regimens (0 versus 1-2)	Yes	
BRAF mutation status at baseline (mutated versus not mutated)		Yes
LDH laboratory results at baseline (normal versus abnormal)		Yes
Histopathology subtype at baseline (acral lentiginous & lentigo maligna versus nodular & superficial spreading versus other)		Yes
Location at baseline (skin versus other locations)		Yes
PD-L1 status at baseline (<1% versus ≥1%)	Yes	Yes
Disease status at study entry (locally advanced versus metastatic)	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 dose escalation, the occurrence of DLT and other safety data will be reviewed by Study Board (SB) to determine RP2D.

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	25-Aug-2021	1.1 Synopsis, 3 Objectives and Endpoints, 9.4.3 Secondary endpoint(s) Definitions of Time to complete response, Time to response, and Duration of response have been revised as follows: • Time to CR defined as the time from the first administration of IMP to the first tumor assessment at which the overall response was recorded as CR that is subsequently confirmed and determined by Investigator per RECIST 1.1 for melanoma participants and when applicable for CSCC participants • Time to Response 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 and determined by Investigator per RECIST1.1 or modified WHO criteria or composite criteria, whichever relevant. • Duration of Response defined as the time from first tumor assessment at which the overall response was recorded as CR or PR that is subsequently confirmed until documented PD determined by Investigator per RECIST 1.1 or modified WHO Criteria for medical photographs or composite criteria when relevant, or death from any cause, whichever occurs first.	For clarification
3	25-Aug-2021	1.1 Synopsis 4.1 Overall Design Observation and Follow-up period have been revised as follows: • Under the definition of End of Treatment and Follow-up for participants who discontinue study treatment without radiological or clinical PD or who complete 35 cycles of treatment without PD, “final” has been added to cohort cut-off • Under the definition of End of Treatment and Follow-up for participants who discontinue study treatment with radiological or clinical PD (per RECIST 1.1 or modified WHO Criteria for medical photographs) or [redacted] the following text “or until start of another anticancer therapy or cohort cut-off, whichever comes first” has been removed • Under the definition of Survival Phone Call Follow-Up Period the following text “or until the last participant to enter Survival Follow-Up has been followed for no more than 3 years” has been replaced by “final cohort cut-off”	For clarification
3	25-Aug-2021	9.5 Interim Analyses The study cut-off date has been replaced by cohort cut off for final analysis.	
3	25-Aug-2021	1.1 Synopsis 4.1 Overall Design 9.3 Populations for Analyses The definition of DLT-evaluable participants has been updated to “all participants in the dose escalation who have been treated and observed for at least 21 days”.	Harmonization per program level approach

Amendment Number	Approval Date	Changes	Rationale
3	25-Aug-2021	9.5 Interim analyses The following text has been added: "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".	Regulatory Authorities (ANSM, HPRA and BfArM) request
3	25-Aug-2021	9.3 Populations for Analyses The definition of efficacy population has been revised to "Efficacy population will include all participants from the exposed population with at least one evaluable post-baseline tumor assessment or who permanently discontinued study treatment".	To characterize efficacy excluding participants newly enrolled
3	25-Aug-2021	9.4.1 General considerations "By dose (as applicable)" has been added to efficacy analyses	For clarification
3	25-Aug-2021	9.4.3 Secondary endpoint(s) 9.4.5 Other safety analyse(s) "When relevant" has been added before "for laboratory variables" in Section 9.4.3.8 and before "the summary statistics (including mean, median, standard error, minimum and maximum) of all vital signs" in Section 9.4.5, respectively.	These analyses will be done as needed following analyses of abnormalities according to NCI-CTCAE grade
3	25-Aug-2021	9.4.5 Other safety analyse(s) "ECG" has been removed from quantitative analyses	Harmonization per program level approach
4	20-Oct-2021	8.3.1 Time period and frequency for collecting AE and SAE information The instruction to stop collecting AE and SAE information should the participant initiate another anticancer therapy was removed. All AEs and SAEs/AESIs are to be collected until 30 days and 90 days, respectively, following cessation of study treatment.	For consistency with Sanofi standards

4 SAMPLE SIZE DETERMINATION

As this study is not intended to explicitly test a hypothesis, calculations of power and Type I error were not considered in the study design. No formal testing procedure is going to be considered.

The study will start with a dose escalation to determine the RP2D of SAR444245 when combined with cemiplimab.

The plan is to treat a total of approximately 80 participants: approximately 40 participants in Cohort A and approximately 40 participants in Cohort B.

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 Cohort A and in Cohort B.

Table 10 - Estimated objective response rate with 90% Clopper-Pearson CI according to number of responders

Number of responders (N=40)	Objective Response Rate in % (90% Clopper-Pearson CI)
18	45.0% (31.5% - 59.1%)
20	50.0% (36.1% - 63.9%)
22	55.0% (40.9% - 68.5%)
24	60.0% (45.8% - 73.1%)
26	65.0% (50.8% - 77.5%)

For each Cohort A and Cohort B individually, with a sample size of 40 study participants, 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

1L: first-line
ADAs: anti-drug antibodies
ADI: actual dose intensity
ASTCT: American Society for Transplantation and Cellular Therapy
CBR: clinical benefit rate
COVID-19: Coronavirus disease 2019
CR: complete response
[redacted]
CSCC: cutaneous squamous cell carcinoma
[redacted]
DLT: dose limiting toxicity
DMC: data monitoring committee
DOR: duration of response
ECG: electrocardiogram
ICI: immune checkpoint inhibitor
IE: intercurrent event
IMP: investigational medicinal product
[redacted]
NAT: new anti-cancer therapy
NCI-CTCAE: National cancer institute common terminology for adverse events
ORR: objective response rate
[redacted]
PDI: planned dose intensity
PD-L1: programmed cell death ligand 1
PFS: progression free survival
PK: pharmacokinetic
PR: partial response
RDI: relative dose intensity
RECIST: response evaluation criteria in solid tumors
RP2D: recommended Phase 2 dose
SAE: serious adverse event
SAP: statistical analysis plan
SB: study board
SD: standard deviation
TEAE: treatment-emergent adverse event
[redacted]
TTR: time to response
WHO-DD: world health organization-drug dictionary

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 cemiplimab) 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 (kg/m^2)
- 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
- Tumor infiltrating lymphocytes in primary tumor
- Stage of the disease

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:

- 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 regimen

- Time to progression of the last 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.

Categories of premedications are:

- 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

Test	Gender	Unit	Lower/upper limit of normal
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

1. Guo W, Wang SJ, Yang S, Lynn H, Ji Y. A Bayesian interval dose-finding design addressing Ockham's razor: mTPI-2. Contemp Clin Trials. 2017;58:23-33.

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