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 lung cancer or pleural mesothelioma**
Protocol number:	**ACT16849**
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 lung cancer or mesothelioma**
Acronym	**Pegathor Lung 202**
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VERSION HISTORY

This statistical analysis plan (SAP) for study ACT16849 is the first version and is based on the amended protocol 03 dated 20-Oct-2021. This section summarizes the major changes to the statistical analysis features in the SAP.

The first participant was enrolled in safety run-in part on 11-Oct-2021. This SAP is approved before the first participant is enrolled in the expansion part.

Table 1 - Major changes in statistical analysis plan

SAP Version	Approval Date	Changes	Rationale	Change from
1	Current version	• Treatment-related TEAEs will be analyzed by overall treatment regimen and not by individual drug as initially planned in the protocol. • Estimand framework has been added for the primary and main secondary efficacy endpoints. • B2 and A3 mentions and combinations are removed	• To assess treatment-related AEs of the regimen as a whole (SAR444245 with other anticancer therapies) • To further characterize the antitumor activity effect that will be estimated. • Combinations with multi-agent chemotherapy have been cancelled in memo #06 dated at 25 May 2022	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-based therapies in participants with non-small cell lung cancer (NSCLC) or mesothelioma.

After a screening period of up to 28 days, participants will be enrolled in one of the four cohorts below:

- **Cohort A1:** participants with PD-L1 TPS ≥50% NSCLC, to receive SAR444245 + pembrolizumab as 1L therapy.
- **Cohort A2**: participants with PD-L1 TPS 1%-49% NSCLC, to receive SAR444245 + pembrolizumab as 1L therapy.
- **Cohort B1**: participants with NSCLC, to receive SAR444245 + pembrolizumab as 2/3L therapy.
- **Cohort C1**: participants with mesothelioma, to receive SAR444245 + pembrolizumab as 2/3L therapy.

The study consists of a safety run-in and core phase for all cohorts, and an expansion phase for Cohorts B1.

The study will start by a safety run-in part with a dose escalation to confirm the dose of SAR444245 when combined with pembrolizumab. Dose escalation will proceed using Modified Toxicity Probability Interval Design (mTPI-2 design, Guo et al 2017 (1). The starting dose will be 24 µg/kg Q3W with a possibility to de-escalate to [redacted] based on the occurrence of dose limiting toxicity (DLT) and overall assessment of safety. The plan is to treat a minimum of 6 DLT-evaluable participants treated at RP2D before starting the core phase. Participants who are enrolled in the safety run-in and treated at the confirmed safe dose will be included in the total number of participants in the core phase for that specific cohort.

In the core phase approximately 40 participants at the confirmed safe dose will be treated per cohort. The results of an interim analysis will decide if the expansion phase will be opened for Cohort B1. Approximately 57 additional participants are planned to be enrolled in the expansion phase to better assess antitumor activity.

A safety run-in will confirm the dose of SAR444245 in combination with pembrolizumab tested in this study.

Participants who fulfill the eligibility criteria of any cohort testing the regimen may be enrolled to the safety run-in of that regimen. After a maximum of 10 participants have been enrolled in one regimen, enrollment will be paused. Once at least 6 participants are evaluable for DLT, safety

data for these participants will be reviewed by the Study Board (SB). If no safety concerns are identified by the SB, participant enrollment will continue. Participants who are enrolled in the safety run-in and treated at the confirmed safe dose will be included in the total number of participants in the core phase for that specific cohort.

After a screening period of up to 28 days, participants will receive treatment until progressive disease (PD), unacceptable adverse event (AE) or other full permanent discontinuation criteria (described in Section 7 of the protocol) or completion of Cycle 35 (if applicable).

1.2 OBJECTIVES AND ENDPOINTS

Table 2 - Objectives and endpoints

Objectives	Endpoints
Primary	
• To determine the antitumor activity of SAR444245 in combination with pembrolizumab.	• Objective response rate (ORR), defined as the proportion of participants who have a confirmed CR or partial response (PR), determined by investigator per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 for Cohort A1, Cohort A2, and Cohort B1; per modified RECIST (mRECIST) for Cohort C1.
Secondary	
• To confirm the dose and to assess the safety profile of SAR444245 when combined with pembrolizumab.	• Incidence of TEAEs, DLTs, SAEs, laboratory abnormalities according to NCI CTCAE V5.0 and ASTCT consensus gradings.
• 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 (for NSCLC) or mRECIST (for mesothelioma). • 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 progressive disease (PD) determined by investigator per RECIST 1.1 (for NSCLC) or mRECIST (for mesothelioma) or death from any cause, whichever occurs first. • Clinical benefit rate (CBR) including CR or PR at any time plus stable disease (SD) of at least 6 months (determined by investigator per RECIST 1.1 [for NSCLC] or mRECIST [for mesothelioma]). • 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 as per RECIST 1.1 (for NSCLC) or mRECIST (for mesothelioma) or death due to any cause, whichever occurs first.

Objectives	Endpoints
• To assess the plasma concentrations of SAR444245 when given in combination with pembrolizumab.	• Plasma concentrations of SAR444245.
• To assess the immunogenicity of SAR444245.	• Incidence of anti-drug antibodies (ADAs) against SAR444245.

1.2.1 Estimands

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

Table 3 - Summary of primary estimands for main endpoints

Endpoint Category (estimand)	Estimands			
	Endpoint	**Population**	**Intercurrent event(s) handling strategy**	**Population-level summary (Analysis and missing data handling)**
Primary objective: To determine the antitumor activity of SAR444245 in combination with pembrolizumab				
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. Confidence interval will be calculated using Clopper Pearson methods
Secondary objective: To assess other indicators of antitumor activity of SAR444245 in combination with pembrolizumab				
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 safety run-in, core and expansion phases. The participants included in the safety run-in, if fulfilling the inclusion criteria of the core/expansion phases and if the planned dose and dosing schedule are the same as in core/expansion phases will be included in the analyses of core/expansion phases.

Table 4 - Populations for analyses

Population	Description
Screened	All participants who signed the informed consent form.
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 pembrolizumab).
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 safety run-in who have been 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 the exposed population with at least one ADA result (positive, negative or inconclusive) after the first dose of study intervention.
Pharmacodynamics (PDy)	All participants from the exposed population with at least one 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 IMPs. 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 per planned arm by cohort, overall by dose or not (if applicable). Some cross-cohort summaries will be presented too. For Cohort B1 expansion phase, results will be presented by core phase and overall phase (combining core phase and expansion phase). Participants enrolled in the safety run-in and treated at the RP2D will be included in the analyses of the core/expansion phases.

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 local radiologist's/Investigator's assessment for all cohorts and the following criteria:

- For Cohort C1: mRECIST
- For other cohorts: RECIST 1.1

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

Confidence intervals (CI) will be two-sided 90% CI for efficacy analyses performed on the core phase and two-sided 95% CI for efficacy analyses performed on the overall phase including core and expansion phases for cohorts with expansion phase (for B1). Confidence intervals 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 tumoral 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 up to first administration of 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 as confirmed complete response (CR) or partial response (PR), determined by investigator.

3.2.2 Main analytical approach

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

- The endpoint is confirmed objective response (OR, ie, confirmed CR or PR).
- The treatment condition is SAR444245 in combination with pembrolizumab.
- The analysis population is the efficacy population.
- Intercurrent events (IEs):
  - 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 (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. 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 pembrolizumab.
- 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 interval 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)** defined as the time from the date of first tumor assessment at which the overall response was recorded as PR or CR that is subsequently confirmed until documented PD before the initiation of any post-treatment anticancer 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 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 will be 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 pembrolizumab.
- 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 CI at specified time points. CIs for KM estimates will be estimated for each treatment group using the Kaplan-Meier method and a 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 5.

Table 5 - 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 CBR 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]

[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 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 + 20 days for pembrolizumab.

The total number of cycles started and number of cycles started by participant 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
- Relative dose intensity (RDI, in %): $100 \times \frac{\text{ADI ([µg/kg/week])}}{\text{PDI ([µg/kg/week])}}$

The total number of doses, 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. RDI will also 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 6, by comparing the current dose level to the previous dose level. If the current dose level is below the dose level interval of the previous dose administration, then the current dose level is considered reduced.

Table 6 - 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 the infusion 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 re-started.
    - Number (%) of participants with at least 1 dose interrupted and not re-started.
  - Number (%) of participants with at least 2 dose interruptions.
- **Dose** (number of doses started will be used as denominator):
  - Number of doses,
  - Number (%) of doses interrupted,
  - 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 Pembrolizumab exposure

The dose information will be assessed by the following:

- Total number of cycles started per participant.
- Duration of Pembrolizumab exposure (in months) is defined by (date of last administration of Pembrolizumab + 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.
- 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 Pembrolizumab exposure, cumulative dose, ADI and RDI will be summarized quantitatively. RDI will also summarized by category if relevant.

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

- Dose omission: is defined as a dose not administered at the scheduled visit.
- Dose interruption: A dose will be considered to be 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 modification:
    - Number (%) of participants with at least 1 dose omission.
  - Number (%) of participants with at least 1 infusion interruption:
    - Number (%) of participants with at least 1 infusion interrupted and restarted.
    - Number (%) of participants with at least 1 infusion interrupted and not restarted.
  - Number (%) of participants with at least 2 infusion 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 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 7.

Table 7 - 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 TEAEs 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 IMP)

The AE summaries of Table 8 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 8 - 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
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 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 8 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 7.

In addition, the following analyses will be done for Adverse Events in 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 Adverse Events in Infusion reaction category, by predefined grouping and other reported PT
- 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 Adverse Events in Infusion reaction category (at the first infusion and subsequent infusions)
- Number (%) of participants with Adverse Events in Infusion reaction category (any episode) at the first and subsequent infusions
- Number (%) of participants with at least one infusion with two episodes of Adverse Events in Infusion reaction category
- Total number of episodes of Adverse Events in Infusion reaction category
- 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 Adverse Events in Infusion reaction category (in days) (by category 1 day/ 2 to 3 days/ More than 3 days/ Not recovered)
- Number (%) of participants with symptoms of Adverse Events in Infusion reaction category (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: neutrophils, lymphocytes, leukocytes, monocytes, basophils, and eosinophils
- Clinical chemistry:
  - Metabolism: glucose, albumin, lipase, and amylase
  - Electrolytes: sodium, potassium, chloride, corrected calcium, bicarbonate and 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, urea. eGFR will be derived by Investigator.
  - Liver function: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), total and direct 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 (ULOQ) will be replaced by ULOQ value.

For hematological parameters and some selected biochemistry parameters, Sanofi 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 potentially clinically significant abnormality (PCSA) and NCI CTCAE 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

PK parameters will include but may not be limited to those listed in Table 9, depending on the IMP and type of PK. [redacted]

Table 9 - List of PK parameters and definitions

Parameters	Definition	[redacted]	Sparse PK SAR444245
C_{trough}	Concentration observed just before intervention administration during repeated dosing		
C_{EOI}	Concentration at end of infusion		X
[redacted]			

Parameters	Definition	Intensive PK SAR444245	Sparse PK SAR444245
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	
CD2	concentration sample taken any time at Day 2 after previous administration		X
CD3	concentration sample taken any time at Day 3 after previous administration		X

These PK parameters will be summarized as indicated in following sections on the PK population. Sparse [redacted]PK of SAR444245 will be analyzed separately.

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.

3.7.1.1.1 Descriptive statistics

The PK variables defined above will be summarized by cycle separately for subjects with sparse PK [redacted], as well as pooling all subjects, using the following descriptive statistics: mean, median, standard deviation, coefficient of variation, minimum, and maximum. In addition, geometric mean and geometric standard deviation will be calculated for concentration parameters. These analyses will be performed by specific subgroups (eg, gender, BMI, age) if appropriate.

Listings of participant accumulation ratios will be provided.

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.

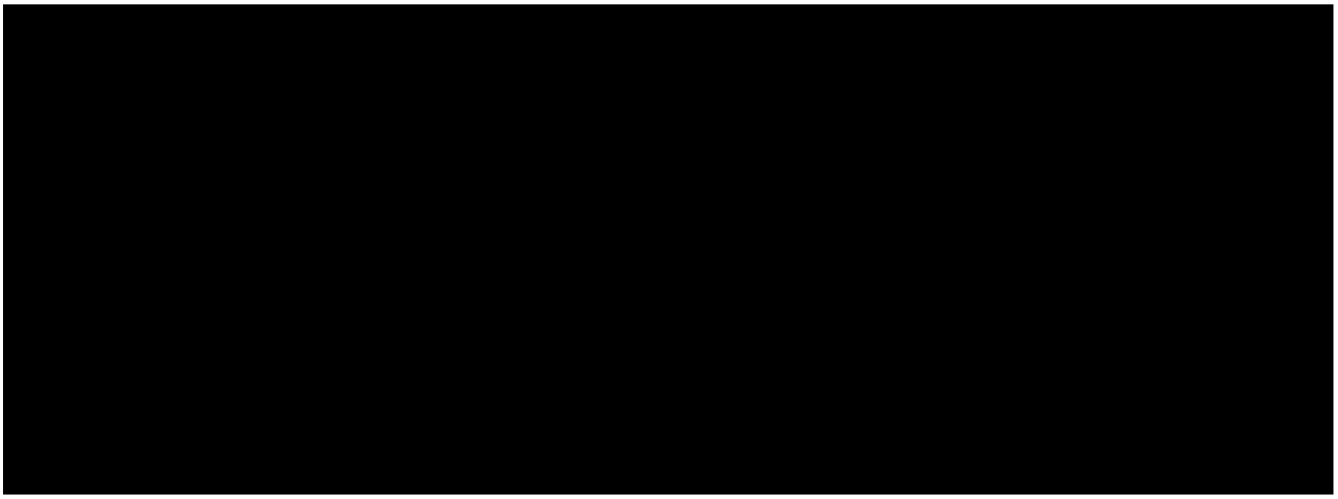
- A positive sample (boosted positive sample for participants with pre-existing ADA) occurring after the TE period will be considered as treatment-induced/boosted ADA if a previous treatment-induced/boosted ADA occurred during the TE period and less than 16 weeks before this sample;

- **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 10 - Subgroup analyses

	A1	A2	B1	C1
Number of prior systemic therapy regimens (1 versus >=2)			Yes	Yes
PD-L1 status at baseline (<1, 1-49% versus >=50%)			Yes	Yes
Squamous vs Non-squamous	Yes	Yes		
Epithelioid vs Non- epithelioid				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

During the core phase, no formal interim analyses are planned. However, the following analyses will be performed:

- At the end of the safety run-in, the occurrence of DLT and other safety data will be reviewed by Study Board to decide about continuation of the dose of SAR444245 of 24 µg/kg or reduction to [redacted] or another lower dose level.
- After the dose is confirmed by the SB, the cumulative safety data for each study intervention across cohorts will be reviewed periodically by the Independent Data Monitoring Committee (IDMC). The enrollment will not be paused or stopped during the safety monitoring unless severe safety concern arises. IDMC will review safety data periodically. Ad hoc IDMC 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 IDMC procedures will be detailed in the IDMC charter and approved by the IDMC 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 study, eg, in each cohort, after 20 participants at the confirmed safe dose have undergone two post-baseline tumor assessments (approximately 18 weeks from the 20 participants are first treated) or have discontinued study treatment, whichever is earlier.

At the end of the core phase, cohorts B1 will have one formal interim analysis when all participants in the core phase have at least 2 post-baseline tumor assessments or discontinued study treatment (whichever occurs first). The Sponsor will decide if the expansion will be initiated based on totality of the data observed.

Therefore, for Cohort A1, Cohort A2, and Cohort C1, the cohort cut-off for the primary ORR endpoint analyses is estimated to be approximately 9 months from the date of the last participant's first infusion in the core phase (to document that last participant response is maintained for 6 months in the core phase). For Cohort B1, the cohort cut-offs for the analyses are as follows:

- IA cut-off: the date on which all participants in the core phase have at least 2 post-baseline tumor assessments or discontinue study treatment (whichever occurs first) or who had documented PD.
- Primary analysis cut-off: the date on which the last participant response is maintained for 6 months in the expansion phase (approximately 9 months from the last participant's first infusion in the expansion phase).

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 the date of cohort last participant in, or when all participants within the cohort have completed the study. After this cut-off date for the final analysis, the participants still receiving study treatment in that specific cohort will be followed up as the cohorts after early termination described in Section 10.1.9 of the protocol.

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
02	05-MAY-2021	Section 1.1 Synopsis: Overall design, Section 4.1 Overall Design, and Section 9.3 Populations for Analyses The following text has been deleted: "and have received at least 80% of the intended Cycle 1 dose".	Regulatory Authority (FDA) request and for clarification
02	05-MAY-2021	The following text has been added to specify the collection of all immune-related adverse events (irAEs) until 90 days: "This does not include irAEs, which will be collected until 90 days following last administration of study treatment regardless of whether or not another anticancer therapy is initiated."	Regulatory Authority (FDA) request

Amendment Number	Approval Date	Changes	Rationale
02	05-MAY-2021	"The posterior probability that the true ORR is greater" has been changed from 20% to 23% to align with the ORR from the combination therapy of docetaxel and ramucirumab. The minimum number of responders has been amended from 11 to 12. The ORR has been changed from 27.5% to 30%.	Regulatory Authority (FDA) request
02	05-MAY-2021	The following text was revised: Progression-free survival is defined as the time from the date of first IMP to the date of the first documentation of objective progressive disease ~~when relevant~~, or death due to any cause, whichever occurs first.	Change made for clarification
03	20-OCT-2021	1.1 Synopsis, 3 Objectives and Endpoints, 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: • 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 (for NSCLC) or mRECIST (for mesothelioma). • 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 progressive disease (PD) determined by investigator per RECIST 1.1 (for NSCLC) or mRECIST (for mesothelioma) or death from any cause, whichever occurs first.	For clarification
03	20-OCT-2021	The cut-off date for the final analysis was defined. The study cut-off date has been replaced by cohort cut-off for final analysis.	For clarification
03	20-OCT-2021	The instruction to stop collecting AE and SAE information should the participant initiate another anticancer therapy was removed. All AEs and SAEs are to be collected until 30 days and 90 days, respectively, following cessation of study treatment.	For consistency with Sanofi standards
03	20-OCT-2021	The efficacy population definition was 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 newly enrolled participants
03	20-OCT-2021	9.4.1 General considerations "By dose (as applicable)" has been added to efficacy analyses.	For clarification
03	20-OCT-2021	Descriptive statistics for laboratory variables and vital signs will be performed only when relevant.	These analyses will be done as needed following analyses of abnormalities according to NCI-CTCAE grade
03	20-OCT-2021	"ECG" was removed from quantitative analyses	ECG data are not collected systematically during the treatment period

4 SAMPLE SIZE DETERMINATION

The study will start with a safety run-in to confirm the dose of SAR444245 when combined with pembrolizumab in a sample of at least 6 participants in each study intervention.

Overall, in the core phase (all cohorts), the plan is to treat approximately 40 participants at the confirmed safe dose per cohort.

In the expansion phase, approximately 57 participants are planned to be treated at the confirmed safe dose in Cohort B1.

Core Phase

Table 11 lists estimated ORR and the corresponding 90% exact CIs by number of responders in each cohort.

Table 11 - Estimated objective response rate and 90% CI for core phase

Number of responders (N=40)	ORR	90% CI for ORR (Clopper-Pearson)
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%)

Expansion Phase

At the end of the core phase of Cohorts B1, the overall efficacy and safety profile will be assessed. The Sponsor may decide to open a 57-participant expansion phase based on the totality of data from the core phase if the posterior probability that the true ORR is greater than 23%, which is considered minimal efficacious signal of interest, is greater than 80% with durable response. Based on a conjugate non-informative prior of beta (0.5, 0.5) at the time of the design of the study, at least 12 responders out of 40 exposed participants at the confirmed safe dose (ORR=30%) need to be observed in the core phase. However, emerging data generated from outside of the study may warrant a different prior to be considered before the formal IA. Analyses based on the total 97 participants at the confirmed safe dose by combining the core phase and expansion phase will be performed for each cohort. Table 12 lists estimated ORR and the corresponding 95% exact CIs by number of responders from a sample size of 97 participants evaluable for activity in each cohort.

Table 12 - Estimated objective response rate and 95% CI for Cohorts B1 (combining core and expansion phases)

Number of responders (N=97)	ORR	95% CI for ORR (Clopper-Pearson)
10	10.3%	(5.1%, 18.1%)
15	15.5%	(8.9%, 24.2%)
20	20.6%	(13.1%, 30%)
25	25.8%	(17.4%, 35.7%)
28	28.9%	(20.1%, 39%)
30	30.9%	(21.9%, 41.1%)

With a sample size of 40 study participants at the confirmed safe dose 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. With a sample size of 97 study participants in total, the probability of observing 1 or more instances of a specific AE with a true incidence rate of 1%, 2%, or 5% is 62.3%, 85.9%, or >99%, 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 antibody
CBR:	clinical benefit rate
[redacted]	
DoR:	duration of response
eCRF:	electronic case report form
IDMC:	Independent Data Monitoring Committee
NCI-CTCAE:	National Cancer Institute Common Terminology For Adverse Events
PD:	progressive disease
PDI:	planned dose intensity
PFS:	progression free survival
PK:	pharmacokinetic
PR:	partial response
RDI:	relative dose intensity
RECIST:	response evaluation criteria in solid tumors
SAP:	statistical analysis plan
SC:	Study Committee
SD:	standard deviation
TEAE:	treatment-emergent adverse event
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 4 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 at least one of the study drugs (SAR444245 and pembrolizumab) while at least one IMP 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/m²)
- 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),
- Diagnosis type,
- Histopathology type,
- 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 (adjuvant, advanced, neoadjuvant, radio-sensitizer)
- Time from last relapse/progression to first IMP administration (months)
- Number of prior lines in advanced settings
- Type of prior anti-cancer therapy (chemotherapy, hormonotherapy, immunotherapy, targeted therapy, Other)
- Intent of last prior anti-cancer therapy (adjuvant, advanced, neoadjuvant, radio-sensitizer)
- Reason for discontinuation of the last prior anti-cancer therapy
- Best response to the last prior anti-cancer therapy
- Time to progression of last prior line (months)
- Duration of last prior line (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 for SAR444245 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 pre-medication are:

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

5.4 APPENDIX 5 SANOFI SPONSOR RANGES

Table 13 - 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 4 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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