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 advanced and metastatic gastrointestinal cancer**
Protocol number:	**ACT16902**
Compound number (INN/Trademark):	**SAR444245**
Study phase:	**Phase 2**
Short Title:	**A study of SAR444245 combined with other anticancer therapies for the treatment of participants with gastrointestinal cancer (Master protocol)**
Acronym	**Pegasus Gastrointestinal 203**
Statistician:	[redacted]**(contractor, Aixial)**
Statistical project leader:	[redacted]
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VERSION HISTORY

This statistical analysis plan (SAP) for study ACT16902 is based on the amended protocol 02 dated 21-Jan-2022.

The first participant was enrolled on 10-Jan-2022. This SAP is approved before the first analysis is conducted.

Major changes in statistical analysis plan

SAP Version	Approval Date	Changes	Rationale	Change from
1	Current version	• Interim analyses section: removed "without enrollment hold"	• The enrollment hold was based on a recommendation from the first program-level Data Monitoring Committee (DMC) meeting held on 18 May 2022, to assesses totality of benefit/risk profile based on both efficacy and safety data extracted from clinical database	Amended protocol 02
		• Estimand framework has been added for the primary and main secondary efficacy endpoints.	• To further characterize the antitumor activity effect that will be estimated.	

1 INTRODUCTION

1.1 STUDY DESIGN

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

This study is developed as a master protocol in order to accelerate the investigation of SAR444245 with various anticancer therapies by identifying early efficacy signals.

The information that is introductory and common to all cohorts is included in the master protocol, and cohort-specific elements are contained in individual substudy protocols. Table 1 presents an overview of substudies and cohorts.

Table 1 - Overview of study cohorts

Substudy	Cohort	Study intervention	Disease
01	A	SAR444245 + pembrolizumab	2-3L ESCC - Regardless of CPS Post-PD1/PDL1
02	B1	SAR444245 + pembrolizumab	1-3L GC/GEJ non-MSI-H CPS ≥1 PD-1/PD-L1 Naïve
02	B2	SAR444245 + pembrolizumab	1-3L GC/GEJ non-MSI-H CPS <1 PD-1/PD-L1 Naïve
02	B3	SAR444245 + pembrolizumab	2-4L GC/GEJ non-MSI-H - Regardless of CPS Post-PD1/PDL1
03	C	SAR444245 + pembrolizumab	2-3Lpost PD1/PDL1 HCC
04	D1	SAR444245 + pembrolizumab	3-6L mCRC non-MSI-H Any *RAS*
04	D2	SAR444245 + cetuximab	3-6L mCRC non-MSI-H *RASwt*

ESCC: esophageal squamous cell carcinoma; CPS: combined positive score; GC: gastric cancer; GEJ: gastro-esophageal junction adenocarcinoma, HCC: hepatocellular carcinoma; 1-3L: first to third line; 2-4L: second- to fourth-line; 2-3L: second to third line; 3-6L: third to sixth line; mCRC: metastatic colorectal cancer; MSI-H: high-level microsatellite instability; PD1/PDL1: programmed cell death 1 or programmed cell death-ligand 1; *RASwt*: *RAS* wild-type RECIST: response evaluation criteria in solid tumors;

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 master protocol) or completion of Cycle 35 (if applicable).

1.2 OBJECTIVE AND ENDPOINTS

Table 2 - Objectives and endpoints - master protocol

Objectives	Endpoints
Primary	
• To determine the antitumor activity of SAR444245 in combination with other anticancer therapies	• 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
Secondary	
• To assess the safety of SAR444245 in combination with other anticancer therapies	• Incidence of treatment emergent adverse events (TEAEs), serious adverse events (SAEs), laboratory abnormalities according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) V5.0 and American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading
• 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 • Duration of response (DoR), defined as the time from first documented 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 death from any cause, whichever occurs first • 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. • 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 or death due to any cause, whichever occurs first
• To assess the pharmacokinetics of SAR444245 in combination with other anticancer therapies	• Plasma concentrations and where applicable PK parameters of SAR444245
• To assess the immunogenicity of SAR444245	• Incidence of anti-drug antibodies (ADAs) against SAR444245
Exploratory	
[redacted]	[redacted]

Objectives	Endpoints
[redacted]	[redacted]

Table 3 - Objectives and endpoints - substudies

Substudy	Objectives	Endpoints
	Secondary	
04 (cohort D2)	• To assess active concentrations of cetuximab when given in combination with SAR444245	• C_{trough} and $C_{end\ of\ infusion}$ of cetuximab
	Exploratory	
[redacted]	[redacted]	[redacted]

1.2.1 Estimands

Primary estimand defined for main efficacy endpoints are summarized in below Table 4. More details are provided in Section 3.

Table 4 - Summary of primary estimand for main endpoints

Endpoint Category (estimand)	Estimands			
	Endpoint	**Population**	**Intercurrent event(s) (IE) handling strategy**	**Population-level summary (Analysis and missing data handling)**
Primary objective: To determine the antitumor activity of SAR444245 in combination with other anticancer therapies				
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 other anticancer therapies				
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 confidence interval 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 confidence interval from Kaplan Meier method.

2 ANALYSIS POPULATIONS

The following populations for analyses are defined.

Table 5 - 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 other anticancer therapies).
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.
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 IMPs in combination (refer to Table 1). For participants enrolled but not treated, the baseline value is defined as the last available value before enrollment.

Unless otherwise specified, analyses will be performed by cohort and overall (if applicable).

All efficacy analyses will be performed on the efficacy population and analyzed by cohort and pooled cohorts (B1 and B2) if relevant.

Objective response rate, as well as all other response-related efficacy endpoints will be primarily derived using the local radiologist's/Investigator's assessment and according to criteria RECIST 1.1.

Central imaging may be done retrospectively if significant activity is observed
(See Section 3.2.3 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 antitumoral response.
- A SD response must be assessed at least 6 weeks after the first IMP administration to be considered as evaluable.

All safety analyses will be performed on the exposed population.

Analysis period

The analysis period will be divided into 3 segments:

- The **pre-treatment period** is defined as the time from when the participants give informed consent to 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 (refer to Table 1)
- 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 (refer to Table 1).

- 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.

In addition, the BOR will 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 (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 is defined as the time from the first administration of IMP to the first tumor assessment at which the overall response was recorded as PR or CR that is subsequently confirmed.

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

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

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

3.3.1.2 Main analytical approach

The time to response will be assessed on the subgroup of participants who have achieved confirmed OR and 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 (refer to Table 1).

- 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 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 6.

Table 6 - 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

Situation	Date of progression or censoring	Outcome	Category
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

[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 (refer to Table 1).

  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 for SAR444245,
  - The last administration date + 20 for pembrolizumab or the last administration date + 6 for cetuximab according to the cohort (refer to Table 1).

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 divided by the theoretical cycle duration expressed in weeks (i.e. 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 7, by comparing the current dose level to the previous dose level. If the current dose level is below the dose level interval of the previous dose administration, then the current dose level is considered reduced.

Table 7 - 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 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 and divided by the theoretical cycle duration expressed in weeks (ie, 3 weeks)
- Relative dose intensity (RDI, in %): $100 \times \frac{\text{ADI (mg/week)}}{\text{PDI (mg/week)}}$

The total number of cycles started, number of cycles started by participants will be summarized by category. Duration of pembrolizumab 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 omission is defined as a dose not administered at the scheduled visit.
- Dose interruption: A dose will be considered as interrupted if pembrolizumab administration is stopped during an infusion regardless of whether the infusion 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 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

3.6.1.4 Cetuximab exposure

The dose information will be assessed by the following:

- Total number of cycles started
- Number of cycles started per participant
- Duration of cetuximab exposure (in months) is defined by (date of last administration of cetuximab + 7 – date of first administration of cetuximab)/30.4375.
- Actual dose (mg/m²)
- Cumulative dose (mg/m²): the cumulative dose is the sum of all actual doses of cetuximab, given from first to last administration

- Actual dose intensity (ADI in mg/m²/week): defined as the cumulative dose divided by the duration of cetuximab exposure (in weeks)
- Planned dose intensity (PDI in mg/m²/week): corresponds to the sum of planned dose started divided by theoretical duration of cetuximab exposure (in weeks)
- Relative dose intensity (RDI, in %): $100 \times \frac{\text{ADI (mg/m}^2\text{/week)}}{\text{PDI (mg/m}^2\text{/week)}}$

The total number of cycles started, number of cycles started by participants will be summarized by category. Duration of cetuximab 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 and second administration will not be counted as a dose reduction. For the third and subsequent cetuximab administrations, dose reduction will be determined using the dose level intervals provided in Table 8, by comparing the current dose level to the previous dose level. If the current dose level is below the dose level interval of the previous dose administration, then the current dose level is considered reduced.

Table 8 - Cetuximab dose reduction criteria

Actual dose level	Dose level interval
250 mg/m²	> 225 mg/m²
Dose level -1 (200 mg/m²)	>175 mg/m² and ≤225 mg/m²
Dose level -2 (150 mg/m²)	>0 mg/m² and ≤175 mg/m²

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

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

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

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 9.

Table 9 - Sorting of AE tables

AE presentation	Sorting rules
SOC, HLGT, HLT and PT	By the internationally agreed SOC order and by alphabetic order of HLGTs, HLTs and PTs.
SOC and PT	By the internationally agreed SOC order and decreasing frequency of PTs [a, b]
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 10 will be generated with number (%) of participants experiencing at least one event. The analyses will be performed for all grades combined and for grades ≥3. The all TEAE summary by Primary SOC and PT (and other safety summaries (eg, SAEs, deaths), if deemed needed after TEAE evaluation) will be performed by trial impact (disruption) due to COVID-19.

Table 10 - Analyses of adverse events

Type of AE	MedDRA levels
All TEAE	Primary SOC, HLGT, HLT and PT
	Primary SOC and PT
TEAE related to IMP (overall) as per Investigator's judgment	Primary SOC and PT
Treatment emergent SAE	Primary SOC and PT
Treatment emergent SAE related to IMP (overall) as per Investigator's judgment	Primary SOC and PT
TEAE leading to permanent full intervention discontinuation	Primary SOC and PT
TEAE leading to permanent partial intervention discontinuation (for each individual drug)	Primary SOC and PT
TEAE leading to death (death as an outcome of the AE as reported by the Investigator in the AE page)	Primary SOC and PT
AE leading to death[a]	Primary SOC and PT
• In context of disease progression[b]	
• In context other than disease progression[c]	
Pre-treatment AE	Primary SOC and PT

Type of AE	MedDRA levels
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 10 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 9.

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 reactions (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.

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

PK parameters will include but may not be limited to those listed in Table 11, depending on the IMP and type of PK. The intensive PK parameters will be calculated using non-compartmental method from SAR444245 concentrations.

Table 11 - List of PK parameters and definitions

Parameters	Definition	Intensive PK SAR444245	Sparse PK SAR444245	Sparse PK cetuximab
C_{trough}	Concentration observed just before intervention administration during repeated dosing			X
C_{EOI}	Concentration at end of infusion		X	X
C_{max}	Maximum concentration observed	X		

Parameters	Definition	Intensive PK SAR444245	Sparse PK SAR444245	Sparse PK cetuximab
C_{last}	Last concentration observed above the lower limit of quantification	X		
t_{last}	Time of the last concentration observed above the lower limit of quantification (ie, C_{last})	X		
AUC_{last}	Area under the plasma concentration versus time curve calculated using the trapezoidal method from time zero to t_{last}	X		
AUC	Area under the concentration versus time curve extrapolated to infinity	X		
R_{ac}	Observed accumulation ratio calculated using the following equation : $R_{ac} = \frac{AUC\ at\ Cycle\ 4\ Day\ 1}{AUC\ at\ Cycle\ 1\ Day\ 1}$	X		
$R_{ac,Cmax}$	Observed accumulation ratio calculated using the following equation : $R_{ac,\ Cmax} = \frac{\mathrm{Cmax}\ at\ Cycle\ 4\ Day\ 1}{Cmax\ at\ Cycle\ 1\ Day\ 1}$	X		

These PK parameters will be summarized as indicated in following sections on the PK population. Sparse and intensive 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 separate for Chinese and non-Chinese subjects, 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.

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 Quality of life analyses

Quality of life analyses of [redacted] will be described in separated document.

[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 12 - Subgroup analyses

	ESCC	GC/GEC			HCC	CRC	
	A	B1	B2	B3	C	D1	D2
Number of prior systemic therapy regimens							
1 vs >=2	Yes			Yes	Yes		
0 vs >=1		Yes	Yes				
2 vs >=3						Yes	Yes
Disease status at entry (locally advanced vs metastatic)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
PD-L1 status at baseline (<1 vs >=1%)	Yes			Yes	Yes	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, for each cohort, in order to support project strategic planning and design of future studies, informal interim analyses will be conducted during the study (eg, after half of the planned number of participants have undergone two post-baseline tumor assessment or have discontinued study treatment, whichever is earlier).

If the predictive probability of concluding a minimum clinical meaningful effect of the study treatment (ORR) at the end of study is <15%, the corresponding cohort will be stopped for futility. Minimum clinical meaningful effect for each cohort is in Table 13. To facilitate the calculation of predictive probability, a minimum informative prior of Beta (0.5, 0.5) is used at the time of the design of the study. However, emerging data generated from outside of the study may warrant a different prior to be considered before this interim analysis.

Table 13 - Minimum clinical meaningful effect

	ESCC	GC/GEC			HCC	CRC	
	A	B1	B2	B3	C	D1	D2
ORR	5%	15%	5%	10%	5%	5%	5%

In addition, the cumulative safety data for each study intervention across cohorts will be reviewed periodically by the Data Monitoring Committee (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. Occurrence of any treatment related G3 or higher AE (excluding lymphocyte count decrease) not resolving within 72 hours in >25% of participants will trigger ad hoc DMC. The DMC procedures will be detailed in the DMC charter and approved by the DMC members.

The cohort cut-off for the primary ORR endpoint analysis is estimated to be approximately 9 months from the date of the last participant first infusion. This would allow the possibility to observe the response of the last participant for 6 months, assuming there is a response at first treatment assessment.

For each cohort, the cut-off date for the final analysis (ie, analysis of secondary objectives and update of primary objective) will be 18 months from cohort LPI. 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 master 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 Master protocol	21-Jan-2022	1.1 Synopsis, 3 Objectives and Endpoints, and 9.4.3 Secondary endpoint(s) 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. • 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 death from any cause, whichever occurs first.	For clarification.
02 Master protocol	21-Jan-2022	1.1 Synopsis and 9.4.3.5 Adverse events Treatment-related TEAEs will be analyzed overall, regardless of the drug	To assess treatment-related AE of the regimen as whole (SAR444245 with other anticancer therapies).
02 Master protocol	21-Jan-2022	9.3 Population of analyses Update of Efficacy population definition	To characterize efficacy excluding participants newly enrolled.
02 Master protocol	21-Jan-2022	9.5 Interim analysis The following sentence has been added "Occurrence of any treatment related G3 or higher AE (excluding lymphocyte count decrease) not resolving within 72 hours in >25% of participants will trigger ad hoc DMC."	For clarity.
02 Substudy 02	12-Jan-2022	1.3 Schedule of activities (SoA) ; 3 Objective and endpoints ; 8.10 Patient-reported outcomes (PRO) 9.4.4.2 Patient-reported outcomes ; Patient-reported outcome assessment have been added. Exploratory objective and endpoints for Patientreported outcomes have been added. New section added. Analysis for PRO endpoints has been added.	To assess patient-reported experience of treatment [redacted] in an exploratory endpoint.

Amendment Number	Approval Date	Changes	Rationale
01 Master protocol	30-Aug-2021	Section 1.1 Synopsis, Section 4.1 Overall design The follow sentence has been deleted “or until start of another anticancer therapy or final cohort cut-off, whichever comes first” for the reason leading to EOT for the participants who discontinue study treatment with PD	For consistency and clarification
01 Substudy 01	30-Aug-2021	Section 9.5 Interim Analyses The following sentences have been added “If the predictive probability of concluding a minimum clinical meaningful effect of the study treatment (ORR of 5%) at the end of study is <15%, the corresponding cohort will be stopped for futility. To facilitate the calculation of predictive probability, a minimum informative prior of Beta (0.5, 0.5) is used at the time of the design of the study. However, emerging data generated from outside of the study may warrant a different prior to be considered before this interim analysis.”	To include stopping rules for futility.
01 Substudy 02	30-Aug-2021	Section 9.5 Interim Analyses The following sentences have been added “For each cohort, if the predictive probability of concluding a minimum clinical meaningful effect of the study treatment (ORR of 15% for cohort B1, 5% for cohort B2, 10% for cohort B3) at the end of study is <15%, the corresponding cohort will be stopped for futility. To facilitate the calculation of predictive probability, a minimum informative prior of Beta (0.5, 0.5) is used at the time of the design of the study. However, emerging data generated from outside of the study may warrant a different prior to be considered before this interim analysis.”.	To include stopping rules for futility.

Amendment Number	Approval Date	Changes	Rationale
01 Substudy 03	30-Aug-2021	Section 9.5 Interim Analyses The following sentences have been added "If the predictive probability of concluding a minimum clinical meaningful effect of the study treatment (ORR of 5%) at the end of study is <15%, the corresponding cohort will be stopped for futility. To facilitate the calculation of predictive probability, a minimum informative prior of Beta (0.5, 0.5) is used at the time of the design of the study. However, emerging data generated from outside of the study may warrant a different prior to be considered before this interim analysis.".	To include stopping rules for futility.
01 Substudy 04	30-Aug-2021	The following sentences have been added "For each cohort, if the predictive probability of concluding a minimum clinical meaningful effect of the study treatment (ORR of 5% for both cohorts) at the end of study is <15%, the corresponding cohort will be stopped for futility. To facilitate the calculation of predictive probability, a minimum informative prior of Beta (0.5, 0.5) is used at the time of the design of the study. However, emerging data generated from outside of the study may warrant a different prior to be considered before this interim analysis."	To include stopping rules for futility.

4 SAMPLE SIZE DETERMINATION

As the study is not intended to explicitly test a hypothesis, calculations of power and Type I error were not considered in the study design.

The plan is to treat approximately 40 participants in each cohort.

Table 14 lists estimated ORR and 90% exact confidence intervals (CIs) by number of responders from a sample size of 40 participants treated.

Table 14 - Estimated objective response rate (ORR) depending on number of responders

Number of Responders (N=40)	Objective Response Rate in % (90% Clopper-Pearson CI)
2	5% (0.9% - 14.9%)
4	10% (3.5% - 21.4%)
6	15% (6.7% - 27.5%)
8	20% (10.4% - 33.2%)
10	25% (14.2% - 38.7%)
12	30% (18.3% - 44.0%)
14	35% (22.6% - 49.2%)

CI: confidence interval

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 each cohort.

5 SUPPORTING DOCUMENTATION

5.1 APPENDIX 1 LIST OF ABBREVIATIONS

ADAs: anti-drug antibodies
ADI: actual dose intensity
ASTCT: American Society for Transplantation and Cellular Therapy
CBR: clinical benefit risk
[redacted]
DMC: data monitoring committee
DoR: duration of response
ECG: electrocardiogram
IE: intercurrent event
IHC: immunohistochemistry
IMP: investigational medicinal product
[redacted]
ITT: intent-to-treat
[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
[redacted]
PFS: progression-free survival
PK: pharmacokinetic
RDI: relative dose intensity
[redacted]
SAP: statistical analysis plan
SD: standard deviation
TEAE: treatment-emergent adverse event
[redacted]
[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 5 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 but at least one is continued
- Permanent **full** intervention discontinuation is defined as the discontinuation of all the study drugs

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

- Enrolled participants
- Enrolled but not 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
  - 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,
- 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:

- Therapy type
- Number of prior regimens
- Intent of prior regimens
- Best response to last regimen
- Intent of last regimen
- Reason for discontinuation of the last regimen
- Time from completion of last regimen of treatment to first study treatment (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 pre-medication are:

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

5.4 APPENDIX 4 SANOFI SPONSOR RANGES

Test	Gender	Unit	Lower/upper limit of normal
Basophils		10^9/L	0 - 0.15
Eosinophils		10^9/L	0 - 0.4
Erythrocytes	Male	10^12/L	4.5 - 5.9
Erythrocytes	Female	10^12/L	4 - 5.2
Hemoglobin	Male	g/L	135 - 175
Hemoglobin	Female	g/L	120 - 160
Hematocrit	Male	v/v	0.41 - 0.53
Hematocrit	Female	v/v	0.36 - 0.46
Leukocytes		10^9/L	4.5 - 11
Lymphocytes		10^9/L	1 - 2
Monocytes		10^9/L	0.18 - 0.5
Neutrophils		10^9/L	1.8 - 3.15
Platelets		10^9/L	150 - 350
Albumin		g/L	35 - 55
Urea Nitrogen		mmol/L	3.6 - 7.1
Chloride		mmol/L	80 - 115
Glucose		mmol/L	3.900001 - 6.999999
Bicarbonate (HCO3)		mmol/L	22 - 29
Potassium		mmol/L	3.5 - 5
Magnesium		mmol/L	0.8 - 1.2
Sodium		mmol/L	136 - 145

Test	Gender	Unit	Lower/upper limit of normal
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

Not applicable.

Signature Page for VV-CLIN-0636106 v1.0
act16902-16-1-9-sap

Approve & eSign	[redacted] Clinical [redacted]

Approve & eSign	[redacted] Clinical [redacted]