Statistical Analysis Plan

A phase 2, open-label, single-arm, multicenter study to evaluate the efficacy and safety of SOT101 in combination with cetuximab in patients with RAS wild-type colorectal cancer (AURELIO-05)

Statistical Analysis Plan Status: Final

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Study interventions:
Product code: SOT101 (previously SO-C101, RLI-15); INN: nanrilkefusp alfa
Cetuximab

Protocol Reference: SC105 (AURELIO-05)
Fortrea Study ID: 000000235712
Sponsor: SOTIO Biotech AG

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Glossary of Abbreviations

Abbreviation	Term
ADA	Anti-Drug Antibodies
AE	Adverse Event
ALT	Aspartate Aminotransferase
ASaT	All-Subjects-as-Treated
AST	Aspartate Aminotransferase
AUC	Area Under the Concentration-Time Curve
AUC_{last}	Area Under the Concentration-Time Curve Over the Last Measurable Timepoint
$AUC_{(0-24h)}$	Area Under the Concentration-Time Curve Over Time 0 to 24 hours postdose
BLQ	Below the Lower Limit of Quantification
BMI	Body Mass Index
BOR	Best Overall Response (according to RECIST)
BRAF	V-raf Murine Sarcoma Viral Oncogene Homolog B1
BSA	Body Surface Area
C_{2h}	Observed Concentration at 2 hours postdose
CBR	Clinical Benefit Rate (according to RECIST)
CI	Confidence Interval
C_{max}	Observed Maximum Concentration
CR	Complete Response
CRF	Case Report Form
COVID-19	Coronavirus Disease of 2019
CT	Computed Tomography
C_{trough}	Observed Trough Concentration
CV	Coefficient of Variation
DBP	Diastolic BP
DLT	Dose-limiting Toxicity
DNA	Deoxyribonucleic Acid
DOR	Duration of Response (according to RECIST)
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EGFR	Epidermal Growth Factor Receptor
Fc	Fragment Crystallizable
HR	Heart Rate
iBOR	Best Overall Response (according to iRECIST)
iCBR	Clinical Benefit Rate (according to iRECIST)
ICF	Informed Consent Form
ICH	International Council for Harmonisation
iCPD	Confirmed Progressive Disease
iCR	Complete Response (according to iRECIST)
IDMC	Independent Data Monitoring Committee
iDOR	Duration of Response (according to iRECIST)
iORR	Objective Response Rate (according to iRECIST)

Abbreviation	Term
iPFS	Progression-free Survival (according to iRECIST)
iPR	Partial Response (according to iRECIST)
iRECIST	Immune-based Therapeutics Response Evaluation Criteria in Solid Tumors
iSD	Stable Disease (according to iRECIST)
iTtP	Time to Progression (according to iRECIST)
iTtR	Time to Response (according to iRECIST)
iUPD	Unconfirmed Progressive Disease
ISC	Internal Safety Committee
K-RAS	Kirsten Rat Sarcoma Viral Oncogene Homolog
LLN	Lower Limit of Normal Reference Range
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NC	Not Calculated
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for AEs
NE	Not Evaluable
N-RAS	Neuroblastoma Rat Sarcoma Viral Oncogene Homolog
ORR	Objective response rate (according to RECIST)
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-free Survival (according to RECIST)
PFS2	PFS on Next-line Anti-cancer Treatment
PK	Pharmacokinetic
PP	Per Protocol
PR	Partial Response
PT	Preferred Term
QTcB	Bazett Corrected QT Interval
QTcF	Fridericia Corrected QT Interval
R_{C2h}, $R_{Ctrough}$	Accumulation Ratio of C_{2h} or C_{trough} on Cycle 3 Day 1/Cycle 1 Day 1
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 Dose
SAE	Serious AE
SAP	Statistical Analysis Plan
SBP	Systolic BP
SD	Standard Deviation
SD	Stable Disease
SI	International System of Units
SOC	System Organ Class
TFLs	Tables, Figures and Listings
T_{last}	Time of the Last Measurable Concentration
T_{max}	Time to Maximum Concentration
TEAE	Treatment Emergent Adverse Event
TESAE	Treatment Emergent SAE
TtP	Time to Progression (according to RECIST)
TtR	Time to Response (according to RECIST)
ULN	Upper Limit of Normal Reference Range

1. Source Documents

The Statistical Analysis Plan (SAP) was written based on the following documentation:

Document	Date	Version
Protocol	09Mar2023	Protocol Amendment 1
eCRF	03May2023	3.0

2. Protocol Details

2.1. Overall Study Design

Study SC105 (AURELIO-05) is a phase 2, open-label, single-arm, multicenter study with an initial safety run-in with 3+3 safety cohorts.

First, 3 patients will be recruited sequentially so that the first administrations of nanrilkefusp alfa to the first and second patients will be 7 days apart and the second and third patients will not be dosed on the same day. These patients will be treated with cetuximab in combination with 9 µg/kg nanrilkefusp alfa, a dose one dose level below the Recommended Phase 2 Dose (RP2D) as determined in study SC103 (AURELIO-03) which evaluated nanrilkefusp alfa at doses up to 12 µg/kg in combination with pembrolizumab.

After the last patient in the 9 µg/kg safety cohort completes the first treatment cycle of 21 days, i.e., the Dose-Limiting Toxicity (DLT) assessment period, an Internal Safety Committee (ISC) will review the safety data. If at least one patient in the initial 9 µg/kg safety cohort experiences a DLT, an additional 3 patients will be recruited into the 9 µg/kg safety cohort. The ISC will review the safety data of these 3 additional patients and decide whether it is safe to increase the dose to 12 µg/kg nanrilkefusp alfa in combination with cetuximab in the second safety cohort or whether the study should proceed with 9 µg/kg nanrilkefusp alfa or with 6 µg/kg nanrilkefusp alfa.

If there are no safety concerns in the initial 9 µg/kg safety cohort, the study will proceed to the second safety cohort and sequentially recruit another 3 patients who will receive 12 µg/kg nanrilkefusp alfa in combination with cetuximab. As in the 9 µg/kg cohort, the first administrations of nanrilkefusp alfa to the first and second patients will be 7 days apart and the second and third patients will not be dosed on the same day. Safety in the 12 µg/kg cohort will be evaluated by the ISC after the last patient completes the DLT assessment period (first treatment cycle of 21 days).

If at least one patient in the 12 µg/kg safety cohort experiences a DLT, an additional 3 patients will be recruited into the 12 µg/kg safety cohort. The ISC will review the safety data of these 3 additional patients and decide whether it is safe to proceed to the main cohort with patients receiving 12 µg/kg nanrilkefusp alfa in combination with cetuximab or whether the study should continue at a lower nanrilkefusp alfa dose.

If there are no safety concerns in the 12 µg/kg safety cohort, the study will proceed to the main cohort and recruit patients who will receive 12 µg/kg nanrilkefusp alfa in combination with cetuximab.

Patients in the initial 9 µg/kg safety cohort may also have a dose increase to 12 µg/kg nanrilkefusp alfa in the next treatment cycle at the discretion of the investigator if there are no safety concerns in the 12 µg/kg safety cohort.

Patients in the safety cohorts who do not fulfill the DLT evaluability criteria for any reason other than DLT during the DLT assessment period will be replaced until at least 3 patients per cohort have completed their DLT assessment period.

In the main cohort of the study patients will be treated with nanrilkefusp alfa in combination with cetuximab in 21-day cycles as described in the study protocol. An Independent Data Monitoring Committee (IDMC) will be established to review safety and efficacy data at certain time intervals, or when the interim analysis for futility is triggered, once the main cohort of the study starts.

Study periods

Participation of each patient will consist of the below study periods.

2.1.1. Study Intervention during Treatment Period

During the treatment period, study interventions will be administered as described in

Table **1** and protocol section 6 until any of the criteria for discontinuation of study interventions is met.

Table 1 Study interventions

Intervention name and type	Dosage formulation	Unit dose strength(s)	Dosage level(s)	Route of administration	Regimen/ treatment period	Sourcing
nanrilkefusp alfa Investigational intervention	Solution for injection	1.3 mg/vial	See section 4.1.1 of the protocol	Subcutaneous	Administration on day 1 (from cycle 2 onwards, ±1 day), day 2 (±1 day), day 8 (±1 day), and day 9 (±1 day) of each 21-day cycle	Provided centrally

Intervention name and type	Dosage formulation	Unit dose strength(s)	Dosage level(s)	Route of administration	Regimen/ treatment period	Sourcing
Cetuximab Investigational intervention	Solution for infusion	5 mg/mL	Initial dose: 400 mg/m^2 body surface area (BSA) as intravenous infusion over 120 minutes Subsequent doses: 250 mg/m^2 as intravenous infusion over 60 minutes	Intravenous infusion via peripheral or central venous line	Administration on day 1 (from cycle 2 onwards, ±1 day), day 8 (±1 day), and day 15 (±1 day) of each 21-day cycle; on day 1 and day 8, cetuximab infusion will start within 30 minutes after nanrilkefusp alfa administration	Provided centrally

After discontinuation of study interventions, patients will be evaluated at an end of treatment visit. This visit will be scheduled within 7 days (+7 days) after the patients' last dose of nanrilkefusp alfa and/or cetuximab (whichever occurs later).

2.1.2. Follow-up

All patients will come to the clinic 30 (±2) days after their last dose of nanrilkefusp alfa and/or cetuximab (whichever occurs later).

Patients will be contacted 90 (+2) days after their last dose of nanrilkefusp alfa and/or cetuximab (whichever occurs later) and then followed up for survival at 3-month (±2 weeks) intervals until the end of the study.

2.2. Study Objectives

2.2.1. Primary Objective

The primary objective of the study is to estimate the antitumor efficacy of nanrilkefusp alfa in combination with cetuximab.

2.2.2. Secondary Objectives

The secondary objectives of the study are:

- To further evaluate the antitumor efficacy of nanrilkefusp alfa in combination with cetuximab
- To assess the safety and tolerability of nanrilkefusp alfa in combination with cetuximab
- To determine the RP2D of nanrilkefusp alfa in combination with cetuximab
- To characterize the Pharmacokinetics (PK) of nanrilkefusp alfa in a subset of patients
- To determine the immunogenicity of nanrilkefusp alfa in combination with cetuximab

2.2.3. Exploratory Objectives

The exploratory objectives of the study are:

- To further evaluate the antitumor efficacy of nanrilkefusp alfa in combination with cetuximab
- To determine the status of immune-, molecular-, and disease-related biomarkers of potential importance
- To determine the impact of the Epidermal Growth Factor Receptor (EGFR) mutational status on efficacy
- To characterize the PK of cetuximab in a subset of patients
- To determine the immunogenicity of cetuximab in combination with nanrilkefusp alfa

2.3. Sample Size and Power

In the safety cohorts the traditional 3+3 design dose escalation will be applied. Therefore, 3 to 6 DLT-evaluable patients per dose level will be included in a cohort. The estimated number of patients is 6-12. The overall sample determined in this trial is 52 patients in efficacy population which includes patients from the safety cohorts and the main cohort.

The total sample size is based on a Bayesian calculation: Markov chain Monte Carlo has been used for the sample size determination. Assuming a desired Objective Response Rate (ORR) for the number of responses, and a uniform prior distribution between 0 and 1, the sample size of 52 patients will ensure at least 80% posterior probability to achieve an effect above the minimal ORR:

- Benchmark ORR: 20%[1]
- Minimal ORR (relative increase, absolute increase): 28.8% (1.44, 8.8%)
- Desired ORR (relative increase, absolute increase): 36.8% (1.84, 16.8%)

2.4. Primary Efficacy Variable

The primary efficacy variable will be the ORR according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1).[2]

2.5. Secondary Efficacy Variables

The secondary efficacy variables will be:

1. ORR according to immune-based Therapeutics RECIST (iRECIST)[3] (iORR)
2. Best Overall Response according to RECIST 1.1 (BOR) and iRECIST (iBOR)
3. Duration of Response according to RECIST 1.1 (DoR) and iRECIST (iDoR)
4. Clinical Benefit Rate according to RECIST 1.1 (CBR) and iRECIST (iCBR)
5. Progression-Free Survival (PFS) according to RECIST 1.1 and iRECIST (iPFS)
6. Time to Response according to RECIST 1.1 (TtR) and iRECIST (iTtR)
7. Time to Progression according to RECIST 1.1 (TtP) and iRECIST (iTtP)

2.6. Exploratory Efficacy Variables

The exploratory efficacy variables will be:

8. PFS on Next-line Anti-cancer Treatment (PFS2)
9. Overall Survival (OS)
10. Assessment of Fragment crystallizable (Fc) gamma receptor polymorphism or presence and changes in T-cell clonality, levels of inflammatory/regulatory cytokines or circulating tumor markers such as circulating tumor Deoxyribonucleic Acid (DNA) at screening and following nanrilkefusp alfa and cetuximab treatment
11. Assessment of the EGFR mutational status at baseline and at disease progression

2.7. Safety Variables

The safety variables will be:

- Treatment-Emergent Adverse Events (TEAEs) according to the National Cancer Institute-Common Terminology Criteria for AEs (NCI-CTCAE[4]), version 5.0
- Safety laboratory findings
- Vital signs
- Electrocardiography findings
- DLTs

2.8. PK and Immunogenicity Variables

- Serum concentrations and calculated PK parameters of nanrilkefusp alfa and cetuximab
  (serum PK samples will be collected from all patients in the initial safety cohorts and from the first 12 patients in the main cohort)
- Incidence, titer, and time course of Anti-drug Antibodies (ADAs) against nanrilkefusp alfa, including neutralizing ADAs
- Incidence, titer, and time course of ADAs against cetuximab, including neutralizing ADAs

3. Analysis Populations

In accordance with ICH E3[5] and ICH E9[6], the following analysis sets will be used for the analyses.

3.1. Screened Population

The Screened Population will consist of all participants who signed the ICF.

The Screened Population will be used for the listing of screen failures and summaries of patient disposition and reasons for screening failures.

3.2. Enrolled Population

The enrolled population is defined as all patients who sign the main study informed consent form and all eligibility criteria are met as confirmed by approver during screening assessments.

This population may include patients who do not receive study treatment.

3.3. All-Subjects-as-Treated Population

The All-Subjects-as-Treated (ASaT) population will consist of all patients exposed to nanrilkefusp alfa or cetuximab.

All safety analyses will be performed on the ASaT population. The ASaT population will also be used for selected efficacy analyses.

3.4. Efficacy Population

The Efficacy population will consist of all patients exposed to the combination therapy for at least one treatment cycle. This is defined as patients with 4 doses of nanrilkefusp alfa and 3 doses of cetuximab in Cycle 1, or patients exposed to both nanrilkefusp alfa and cetuximab in Cycle 1 who started Cycle 2.

This will be the main population for the analyses of the primary endpoint and secondary efficacy endpoints.

3.5. Per Protocol Population

The Per Protocol (PP) population will consist of all patients who had at least one full treatment cycle of nanrilkefusp alfa and cetuximab (with 4 doses of nanrilkefusp alfa and 3 dose of cetuximab in Cycle 1), did not violate any eligibility criteria, and did not have any relevant major protocol deviations.

Protocol deviations are defined as any change, divergence, or departure from the study design or procedures defined in the study protocol. Important protocol deviations are a subset of

protocol deviations which may significantly impact the correctness, accuracy, and/ or reliability of the study data or that may significantly affect a patient's rights, safety, or well-being. Section 3.5.1 details the deviations.

3.5.1. **Important Protocol Deviations Leading to Exclusion from the PP Population**

Deviations from the protocol, as defined in the protocol and/or protocol deviation plan, will be documented by the study monitors and project management throughout the study period.

Only those important protocol deviations considered to have a major effect on efficacy will lead to complete exclusion of the patient from the PP population. For the purposes of this study important protocol deviations leading to exclusion from the PP population will be defined. Criteria which require clinical or medical monitoring interpretation will be reviewed prior to database lock during data review meetings. All important protocol deviations leading to exclusion from the PP population occurring during the study will be reviewed and approved by sponsor prior to database lock in a separate document.

3.6. PK Population

The PK population will consist of all patients who are PK-evaluable, defined as all patients in the ASaT who had at least 1 post-dose concentration measurement above the Lower Limit of Quantification (LLQ).

3.7. Special Subpopulations

Not Applicable.

4. Data Handling

4.1. Time Points and Visit Windows

4.1.1. General Definitions

The study treatment defined is the combination of nanrilkefusp alfa 9 µg/kg or 12 µg/kg subcutaneously and 400 mg/m^2 or 250 mg/m^2 cetuximab IV infusion.

All assessment days will be related to the first day of first dose of study treatment. Start of study treatment is defined as the date and time of first dose of either nanrilkefusp alfa or cetuximab, whichever occurs earliest. Per protocol this should be nanrilkefusp alfa.

General Definition	nanrilkefusp alfa	Cetuximab
Study Day 1	Day 1 is the first dose of study treatment . Relative days after Day 1 are calculated as (assessment date – Day 1 date) + 1. Relative days prior to Day 1 are calculated as (assessment date – Day 1 date). The day prior to Day 1 is Day -1. Day 0 is not defined.	
Date of the First Dose	As per Exposure CRF (First date from Administration date) Minimum of first dose of nanrilkefusp alfa and start date of the infusion for the first dose of cetuximab	As per Exposure CRF (First date from Administration date)
Date of the Last Dose	As per Exposure CRF (Last date from Administration date) Maximum of last dose nanrilkefusp alfa and end date of the infusion for the last dose of cetuximab.	As per Exposure CRF (Last date from Administration date)
Treatment Cycle	As per CRF	
Treatment Day	As per CRF	
Change from baseline	Visit value – baseline value	
Percentage change from baseline	100 * (visit value – baseline value) / baseline value	

4.1.2. Screening Period

For all patients, the screening period is defined as the period from time of signing ICF to the first dose of treatment (nanrilkefusp alfa or cetuximab) (before day 1 of cycle 1). For some variables, data from more than one assessment within the screening period can be collected prior to the first dose of treatment (nanrilkefusp alfa or cetuximab).

The baseline value is defined as the last non-missing value collected before the first dose of study treatment (nanrilkefusp alfa and/or cetuximab) in the screening period. However, for K-RAS and N-RAS parameters as well as eGFR mutation status which come from Biopsy performed within 3 months prior to first dose will also be considered as baseline values.

4.1.3. Treatment Period

Data collected at Day 1 will be assigned to the Treatment Period unless the time (HH:MM) of data collection and time (HH:MM) of first dose of treatment are both recorded and the data collection time is before the time of first dose of treatment. In this case, the assessment will be assigned to the screening period. If the time (HH:MM) of data collection is not recorded but the protocol and/or eCRF includes an instruction to the effect that all Day 1 assessments are to be performed prior to the first dose of treatment, the data collected at Day 1 will be assigned to the screening period. However, adverse events and medications starting on Day 1, will be assigned to the Treatment Period.

The treatment period is defined from the day of the start of study treatment to the day prior to the end of treatment visit , the end of study date, or start of new anti-cancer therapy, whichever is earliest. Date of last contact collected on the 'Survival Status' eCRF where status is 'dead can be after end of study if the contact was with family of subject, but the latest end of study date for a 'dead' patient is the death date of the patient.

4.1.4. Visit Windows

All data will be analyzed using nominal study visit as defined in the Study Schedule and eCRF. No visit windows will be applied for summary and analysis except for tumor assessment. Repeated and unscheduled measurements will be included in the listings but not be used for statistical analyses and summaries, except for the derivation of minimum/maximum values post-baseline. All tumor assessments will be considered for the time-to-event analysis.

Unscheduled visits will be identified with a numbering system that reflects the cycle they occur in by comparing the visit date against the scheduled visits and numbering in order of unscheduled visit e.g. Unscheduled Cycle 1 Day 1.01, Unscheduled Cycle 1 Day 8.01 etc. Unscheduled visits occurring on the same day as other visits will not be used in the analysis by timepoint.

Visit window for the Tumor Assessment

Additionally, for the purposes of summarizing target lesions by scheduled week, labels for assessments falling into the scheduled week of study will be derived e.g. 'Week 6 assessment (Weeks 4 to 8)', 'Week 12 assessment (Weeks 10 to 14)' etc., by assigning the assessments within the protocol specified window of every 6 weeks ± 2 weeks (e.g. for Week 6 : C1D1 date + 28 <= Tumor assessment date <=C1D1 date + 56). Labels for assessments falling outside of the assessment windows would be labelled 'Not Assigned'. In the case of multiple tumor assessments in a time window, evaluable assessments closest to the planned assessment time (or the closest non-evaluable assessment if all non-evaluable) will be considered the scheduled assessment. In the case of two assessments within a window being exactly the same distance from the centre of the window, the earliest assessment will be assigned as the scheduled assessment. Contributing assessments (e.g. target lesion assessment) should be labelled consistently with the overall tumor assessment.

4.2. Handling of Dropouts, Missing Data, and Outliers

4.2.1. Handling of Missing Efficacy Data

Patients with missing data for the efficacy endpoints of ORR, iORR, CBR and iCBR will be classified as non-responders, if not otherwise specified.

Patients with missing data for the efficacy endpoints of DoR, iDoR, PFS, iPFS, TtR, iTtR, TtP, iTtP, PFS2, and OS at the end of trial will be regarded as censored as described in Section 5.5.3.

4.2.2. Handling of Missing Safety Data

In general, missing clinical laboratory data, vital signs, and Electrocardiogram (ECG) data will not be imputed. Unknown or partial medication and AE date imputations are given below and to be used only for the assessment of prior / concomitant status for medications and treatment-emergent status for AEs.

4.2.3. Handling of Partial and Missing Dates for Adverse Events, Prior / Concomitant Medications/Procedures

Missing or Partial Adverse Event and Prior / Concomitant Medication/Procedure Start Dates

Missing and / or incomplete dates for medications, procedures and AEs are imputed in a manner resulting in the earliest onset or the longest duration during the Treatment Period, whilst ensuring that the start date does not occur after the stop date. The stop date will not be imputed if the medication or AE is "Ongoing". Technically, this will be done as follows:

For a missing/incomplete start date/time the earliest date/time of the following will be imputed:

- The later date of: the earliest possible start date / time, and the date / time of first dose of treatment.
- The latest possible start date/time.
- The latest possible stop date/time.

For a missing/incomplete stop date/time the later date/time of the following will be imputed:

- The earlier date/time of the latest possible stop date/time and the date/time of last dose of treatment.
- The earliest possible stop date/time.
- The earliest possible start date/time.

Here, the earliest possible date/time is defined as:

- The date/time itself if available.
- The date/time of the first day of the month at 00:00hrs, if month and year are available but the day/time is missing.
- The date/time of the first day of the year at 00:00hrs, if year is available but day/time and month are missing.
- 00:00hrs on the day of informed consent, if the date/time is completely missing.

The latest possible date/time is defined as:

- The date/time itself if available.
- The date/time of the last day of the month at 23:59hrs, if month and year are available but the day/time is missing.
- The date/time of the last day of the year at 23:59hrs, if year is available but day/time and month are missing.
- 23:59hrs on the date of last known date on the study for the patient plus one year, if the date/time is completely missing.

4.2.4. Handling of Partial and Missing Dates for New Anti-Cancer Therapy

Incomplete start dates of follow-up anti-cancer therapy will be imputed as follows:
If only ‘day’ is missing, then impute with the first day of the month.
If ‘day’ and ‘month’ are missing and ‘year’ is not missing and equal to year of last dose, then impute as date of last dose.
Else if ‘day’ and ‘month’ are missing and ‘year’ is not missing and before year of last dose, then impute as 31st December of that year.
Else if ‘day’ and ‘month’ are missing and ‘year’ is not missing and after year of last dose, then impute as 1st January of that year.

If the imputed start date is greater than the last contact date, then set to the last contact date.

4.2.5. Handling of Partial and Missing Death Date

Incomplete dates of death will be imputed as follows:
If only 'day' is missing, then impute with the first day of the month.
If 'day' and 'month' are missing and 'year' is not missing and is the same as the year of the last contact date, then impute as the date of the last contact +1 day.
If 'day' and 'month' are missing and 'year' is not missing and is greater than the year of the last contact date, then impute as 1st January of that year.
If the imputed death date is less than the last contact date, then set to the last contact date + 1 day.

4.2.6. Handling of Partial and Missing Diagnosis Date

The partial start date for initial diagnosis will be assigned to 15th day of the month (if only day is missing) or July 1st (if both month and day are missing).

For completely missing dates no imputation will be performed.

4.2.7. Handling of Partial and Missing Laboratory Data

Missing laboratory data will not be imputed. However, laboratory values of the form of "< x" (i.e., below the lower limit of quantification) or "> x" (i.e., above the upper limit of quantification) will be imputed as "x" for the purpose of calculation of summary statistics and comparing to normal ranges. These values will still be displayed as "< x" or "> x" in the listings.

4.2.8. Handling of Serum PK Concentrations for Study Treatment that are Below the Lower Limit of Quantification

Serum PK concentrations for Study Treatment that are Below the Lower Limit of Quantification (BLQ) will be handled as follows for descriptive statistics:

- For individual data listings, values that are BLQ (*add actual BLQ for nanrilkefusp alfa and cetuximab in ng/mL here)* will be reported as < LLOQ where LLOQ will be replaced by the actual value for LLOQ for the specific PK assay.
- Values that are BLQ will be set to 0 for the calculation of summary statistics by treatment at each scheduled time point (number of patients in analysis set (N), number of patients with data available (n), arithmetic mean, geometric mean, arithmetic SD, geometric coefficient of variation (%CV), 95% confidence interval (CI), median, min, and max).
- If there are less than 3 quantifiable values in a data series, only the minimum, maximum and n will be presented. The other summary statistics will be denoted as not calculated (NC).

- BLQ results (treated as 0) are in a series of summarized data, geometric mean and CV% will be reported as NC.
- Arithmetic mean or median values that are BLQ presented as 0.
- If a *predose* concentration is missing prior to the first dose of Cycle 1 Day 1, the values will be set to zero.

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5. Statistical Methods

5.1. General Principles

All data processing, summarization and analyses will be performed using Fortrea's SAS Environment / Version 9.4 (or later) of the SAS® statistical software package.

The analyses will be descriptive; no formal testing of statistical hypotheses is planned.

Summary statistics:

The default summary statistics for quantitative variables will be the number of observations (n), mean, Standard Deviation (SD), median, minimum (min) and maximum (max), for those patients with data. For qualitative variables, the number (n) and percentage (%) of patients with non-missing data per category will be the default summary presentation, and where appropriate and present, the number of missing values as a "Missing" category. Number of patients in the analysis population will be used as denominator for percentages calculation, unless stated otherwise in TFLs.

Time-to-event endpoints will be summarized using Kaplan-Meier (KM) method. Estimation of median time and the associated 95% Confidence Interval (CI) will be provided using log-log transformation. Number of events, number of censored patients and descriptive statistics [25th and 75th percentiles, minimum and maximum] for time-to-event endpoints will be also provided. The KM curves will be graphically displayed.

Time conversion:

The following conversion factors will be used to convert days into months or years:

1 week = 7 days, 1 month = 30.4375 days, 1 year = 365.25 days.

Laboratory data:

All laboratory clinical safety and urine test results will be received from the local laboratories, and the results will be provided in both Standard Internal (SI) and conventional units. For the TFLs, the results will be summarized or presented in International System of Units (SI) units. Refer to Appendix of the TFLs mock shells for the SI unit corresponding to each laboratory test. Biomarkers, inflammatory cytokines and PK/ADA results will be received from the central laboratories.

Tables, Figures, and Listings (TFLs):

In the listings, laboratory values converted from conventional to International System of Units (SI) units will be reported to the same precision as values originally recorded as SI. Derived values for change/ percent changes in target lesions, and all safety endpoints will be rounded with one decimal place.

Refer to Appendix of the TFL shells for the precision level in which each laboratory test is reported by the central laboratories.

Specifications for table, figures and data listing formats can be found in the TFL shells specifications for this study. Please refer to "2. General Format Guidelines" section within TFL shells for more details on presentation of results.

5.2. Patient Disposition and Data Sets Analyzed

Patient disposition will be summarized by cohort and overall, where appropriate, for the screening population on assigned treatment. The following information will be reported:

- Number and percentage of Screen Failure patients with the reason;
- Number and percentage of patients for the following categories:
  - Enrolled ,
  - Treated ,
  - Not Treated ,
  - Discontinued study treatment (nanrilkefusp alfa, cetuximab, or both),
  - Reasons for study treatment discontinuation,
  - Ongoing in the study,
  - Completed the study,
  - Discontinued the study,
  - Reasons for study discontinuation.
  - Number and percentage of patients included in, and excluded from efficacy population, PP population, and PK population together with the reasons for exclusion from the population;
- Number and percentage of patients at each country/site (ASaT population using assigned treatment will be used for this summary);

A patient will be regarded as having completed the study if the Reason for Completion/Discontinuation on the End of Study eCRF form is "Study completed as per Protocol". A patient will be considered as having discontinued the study if Reason for Completion/Discontinuation is not "Study completed as per Protocol" and not Missing study discontinuation. Otherwise, the patient will be considered as ongoing study. The date of 'End of Study eCRF form' will be used for the definition of end of study date. In case a patient is death the date needs to be equal to Death Details eCRF form is "What was the subject's date of death?".

A listing of all patients with their treatment and study completion status, including the respective reasons for treatment and study discontinuation will be presented for the enrolled population.

A listing of all screen failed patients with their reasons for screen failure will be presented for the screening population. A separate listing of patients who failed at least one

inclusion/exclusion criteria including a text description of the criterion failed will be presented for the screening population.

A listing of all patients excluded from efficacy population, PP population or pharmacokinetics population will be presented for the enrolled population.

5.3. Protocol Deviations

All important protocol deviations leading to exclusion from the PP Population (see Section 3.5.1) will be summarized for the ASaT population overall as described below:

- The number of unique patients with at least one important protocol deviation which led to exclusion from the PP Population as well as the number of patients in each important protocol deviation category will be presented by default descriptive summary statistics for categorical variables.

A listing of all patients with one or more important/non important protocol deviations will be presented for the enrolled population. In addition, a listing of the patients affected by Coronavirus Disease of 2019 (COVID-19) and the type of COVID-19 disruption will be provided for the enrolled population, if applicable.

5.4. Demographic and Other Baseline Characteristics

5.4.1. Demographic Characteristics

Demographic characteristics will be summarized for the ASaT population as described below. All missing data will be presented as part of a missing category, if appropriate. Standard descriptive statistics will be presented for the continuous variables of:

- Age (years)

Total counts and percentages of patients will be presented for the categorical variables of:

- Age group (years):
  - < 18
  - >= 18 to < 65
  - >= 65 to < 85
  - >= 85
- Sex
  - If female, Childbearing potential (Yes/ No)
    - If No, Reasons
- Race
- Ethnicity

Demographic Characteristics analyses will also be repeated in the Efficacy Population as well as the Per Protocol Population and listed for the screened population.

5.4.2. Baseline Characteristics

Baseline characteristics will be summarized for the ASaT as described below. All missing data will be presented as part of a missing category, if appropriate.

Standard descriptive statistics will be presented for the continuous variables of:

- Height (cm) at baseline
- Weight (kg) at baseline
- BSA (m^2) at baseline
- Body Mass Index (BMI) (kg/m^2) at baseline, derived as Weight (kg) at baseline/Height^2 (cm^2) at baseline
- Eastern Cooperative Oncology Group (ECOG) at baseline

No formal tests of statistical significance will be performed on the demographic and baseline characteristics data.

Baseline Characteristics analyses will also be repeated in the Efficacy Population as well as the Per Protocol Population.

Baseline characteristics will be listed for the screened population.

5.4.3. Cancer History

Cancer History analyses will be summarized for the ASaT.

Standard descriptive statistics will be presented for the continuous variables of:

- Initial diagnosis to Screening: time from initial diagnosis of cancer to screening defined as screening date – initial diagnosis date + 1.
- Initial diagnosis to start of treatment: time from initial diagnosis of cancer to first dose defined as First dose date – initial diagnosis date + 1.
- Metastatic diagnosis to start of treatment: time from metastatic diagnosis to first dose defined as First dose date – metastatic disease date + 1.
- Latest disease progression to start of treatment: time from latest disease progression to first dose defined as First dose date – latest disease progression date + 1.
- Number of previous lines of therapy

Total counts and percentages of patients will be presented for the categorical variables of:

- Site of primary tumor and sites of metastatic disease
- Stage at study entry: primary tumor (T) stage, regional lymph nodes (N) stage, distant metastasis (M) stage, and staging

- Histology/ Cytology results and type
- Prior mutation/ Expression status of Kirsten rat sarcoma viral oncogene homolog (K-RAS), Neuroblastoma rat sarcoma viral oncogene homolog (N-RAS), V-raf murine sarcoma viral oncogene homolog B1 (BRAF) and EGFR
- Number of previous lines of therapy (continuous and categorical)
- Previous treatment with EGFR inhibitors
- Response of previous treatment with EGFR inhibitors

Cancer History analyses will also be repeated in the Efficacy Population as well as the Per Protocol Population.

Cancer History will be listed for the screened population.

5.4.4. **Medical History**

Medical history is defined as any condition, with the exception of the study indication, that the patient may have had prior to enrollment in the study, including any chronic conditions diagnosed prior to entry in the study.

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) [most recent version at time of DB lock] and will be presented by System Organ Class (SOC) and Preferred Term (PT) and total. The SOCs and PTs are to be sorted by descending SOCs and descending PTs in the total column.

Medical history records will be summarized for the ASaT population by overall as follows:

- The number and percentage of patients with at least one medical history record will be presented.
- The number and percentage of patients with at least one medical history record within each primary SOC and PT will be presented. The summary will be sorted using the descending order for SOC and using descending order of overall numerical counts for PT. Where terms tie, these will be sorted alphabetically.

Medical history records will be listed by-patient and within-patient by medical history start date for the screened population.

5.4.5. Prior and Concomitant Medications

All medications will be coded using the Format B3G [most recent version at time of DB lock], Anatomical Therapeutic Chemical (ATC) Classification codes.

Prior medications and concomitant medications are defined as follows:

- Prior medication is defined as those taken prior to the first dose with a stop date and time prior to the start of the Treatment Period.

- Concomitant medications are those with a start date and time on or after the start of the Treatment Period, or those with a start date and time before the start of the Treatment Period and either a stop date and time on or the start of the Treatment Period, or are ongoing at the end of the study.

See Section 4.2.3 for imputation of missing or partial dates for medication.

Prior and concomitant medications will be summarized separately for the ASaT population overall as follows:

- The number and percentage of patients with at least one prior/concomitant medication will be presented.
- The number and percentage of patients with at least one prior/concomitant medication within each Anatomical Group (ATC Level 1), Therapeutic Subgroup (ATC Level 2), and preferred term will be presented. The summary will be sorted using numerical counts by descending order of Anatomical Group, then descending order of Therapeutic Subgroup, then descending order of preferred term in the total column. Where groups or terms tie these will be sorted alphabetically.

Prior medications and concomitant medications will be listed separately for the enrolled population. In the listings the relative start and stop day of prior/concomitant medication use will be calculated relative to the first dose date and time of treatment and will be presented for those patients who received at least one dose of treatment. If the concomitant medication is "Ongoing" it will be indicated as such in the listing and the relative stop day will not be calculated. Only original dates will be presented in the listing even though the relative day may be based on an imputed date.

5.4.6. Prior and Concomitant Procedures

All procedures will be coded using the MedDRA dictionary [most recent version at time of DB lock] and presented by System Organ Class (SOC) and Preferred Term (PT). The SOCs and PTs are to be sorted by descending SOCs and descending PTs.

Prior procedures and concomitant procedures are defined as follows:

- Prior procedure is defined as those done prior to the first dose with a stop date and time prior to the start of the Treatment Period.
- Concomitant procedure are those with a start date on or after the start of the Treatment Period, or those with a start date before the start of the Treatment Period and either a stop date on or the start of the Treatment Period, or are ongoing at the end of the study.

See Section 4.2.3 for imputation of missing or partial dates for procedure.

Prior and concomitant procedures will be summarized separately for the ASaT population overall as follows:

- The number and percentage of patients with at least one prior/concomitant procedure will be presented.

- The number and percentage of patients with at least one prior/concomitant procedure within each SOC and PT.

Prior procedures and concomitant procedures will be listed separately for the enrolled population. In the listings the relative start and stop day of prior/concomitant procedures use will be calculated relative to the first dose date of treatment and will be presented for those patients who received at least one dose of treatment. If the concomitant procedure is "Ongoing" it will be indicated as such in the listing and the relative stop day will not be calculated. Only original dates will be presented in the listing even though the relative day may be based on an imputed date.

5.4.7. Prior Radiation Therapy

Number and percentage of patients having prior radiation therapy will be summarised within each primary SOC and PT for the ASaT, Efficacy, and PP populations as a part of prior non-systemic anti-cancer therapy.

Prior radiation therapy data will be listed for the enrolled population as a part of prior non-systemic anti-cancer therapy.

5.4.8. Prior Anti-Cancer Surgery

Number and percentage of patients having prior anti-cancer surgery will be summarised within each primary SOC and PT for the ASaT, Efficacy, and PP populations by treatment group and overall as a part of prior non-systemic anti-cancer therapy.

Prior Anti-cancer surgery data will be listed for the enrolled population as a part of prior non-systemic anti-cancer therapy.

5.4.9. Prior Systemic Anti-Cancer Therapy

Number and percentage of patients having prior systemic anti-cancer therapy will be summarised within ATC Level for the ASaT, Efficacy, and PP populations by treatment group and overall as a part of prior systemic anti-cancer therapy.

Prior systemic anti-cancer therapy data will be listed for the enrolled population as a part of prior systemic anti-cancer therapy.

5.4.10. Subsequent Radiation Therapy

Subsequent Radiation therapy data will be listed for the enrolled population as a part of subsequent non-systemic anti-cancer therapy.

5.4.11. Subsequent Anti-Cancer Surgery

Subsequent Anti-Cancer Surgery data will be listed for the enrolled population as a part of subsequent non-systemic anti-cancer surgery.

5.4.12. Subsequent Systemic Anti-Cancer Therapy

Subsequent Systemic Anti-Cancer therapy data will be listed for the enrolled population as a part of subsequent systemic anti-cancer therapy.

5.5. Efficacy

Only tumor assessments prior to or at the date of initiation of further-line therapy and using CT scan or MRI will be used for the evaluation of tumor response.

In case of a confirmed response or disease progression, the date of the first tumor assessment evaluated as response or progression will be used for the time-to-event variables.

Up to the first iUPD, the RECIST 1.1 disease response assessment will be derived from the iRECIST response assessment form as follows:

Table 2 Derivation of RECIST 1.1 Disease Response from iRECIST 1.1

iRECIST	RECIST 1.1
iCR	CR
iPR	PR
iSD	SD
iUPD	PD
Non-iCR/Non-iUPD	Non-CR / Non-PD
NE	NE

After the first iUPD, the RECIST 1.1 overall response will no longer be derived.

All efficacy data endpoint will be listed on the enrolled population, with the exception of time to event analyses where the ASaT population will be used.

Overview of Tumor Assessments with a swimmer plot per RECIST 1.1 and iRECIST 1.1 will be displayed graphically for ASaT population.

5.5.1. Primary Efficacy Analysis

The ORR is defined as the proportion of patients with Complete Response according to RECIST 1.1 (CR) or Partial Response according to RECIST 1.1 (PR). ORR will be analyzed in the efficacy population and presented as a point estimate along with 95% Clopper-Pearson CI. Patients with missing data will be considered as non-responders.

To determine the ORR, the BOR (see Section 5.5.3.1) of each patient will be computed according to RECIST v1.1 criteria.

ORR according to RECIST 1.1 will also be listed for enrolled population.

5.5.2. Sensitivity for the Primary Analyses

Primary efficacy analysis will be repeated for ASaT and PP populations.

Primary efficacy analysis will be repeated where patients with missing data will be excluded from the analysis.

5.5.3. Secondary Efficacy Analysis

5.5.3.1. BOR and iBOR

The BOR and iBOR are defined as the best response from the start of study treatment until the first documented disease progression, death, or start of new anti-cancer therapy. It will be summarized with counts and percentages in the efficacy populationand will be repeated for ASaT and PP populations.

This will also be repeated in the efficacy population where patients with missing data will be excluded from the analysis.

Stable Disease according to RECIST 1.1 (SD) and Stable Disease according to iRECIST (iSD) needs to last at least 6 weeks from the start of study treatment, if not, at least one follow-up scan is required to declare stable disease.

BOR according to RECIST and iRECIST as well as the Overall Response will also be listed for enrolled population.

For BOR each patient will be assigned one of the following categories (from best response to worst response): CR, PR, SD, PD, NE:

Step	Condition
Step 1: BOR of CR If a BOR of CR is not determined, Step 2 will be performed.	At least two consecutive determinations of CR more than 4 weeks apart, or if not consecutive, with no other assessment between the two determinations other than unable to evaluate (NE), CR.
Step 2: BOR of PR If a BOR of PR is not determined, Step 3 will be performed.	At least two consecutive determinations of PR or CR, more than 4 weeks apart, or if not consecutive, with no other assessment between the two determinations other than NE, CR, PR.
Step 3: BOR of SD If a BOR of SD is not determined, Step 4 will be performed.	At least one SD assessment (or better), ≥ 6 weeks (≥ 42 days) after baseline; if not, at least one follow-up scan (i.e., consecutive scan) evaluated as SD (or better) is required

	to determine a BOR of SD. If not consecutive scans, with no other assessment between the two determinations other than NE, CR, PR, SD.
Step 4: BOR of PD If a BOR of PD is not determined, Step 5 will be performed.	At least one (i.e., any) PD after baseline.
Step 5: BOR of NE	Measurable disease at baseline, but not all or any target lesions have been evaluated, or if derivation of BOR from Step 1 to 5 does not apply. Non-measurable disease at baseline will also result in BOR of NE.

For iBOR each patient will be assigned to one of the following categories (from best to worst responses): iCR, iPR, immune Stable Disease (iSD), immune Confirmed Progressive Disease (iCPD), immune Unconfirmed Progressive disease (iUPD), or Not Evaluable (NE) at each timepoint:

Step	Condition
Step 1: iBOR of iCR If an iBOR of iCR is not determined, Step 2 will be performed.	At least two consecutive determinations of iCR more than 4 weeks apart, or if not consecutive, with no other assessment between the two determinations other than unable to evaluate (NE), iCR.
Step 2: iBOR of iPR If an iBOR of iPR is not determined, Step 3 will be performed.	At least two consecutive determinations of iPR or iCR, more than 4 weeks apart, or if not consecutive, with no other assessment between the two determinations other than NE, iCR, iPR.
Step 3: iBOR of iSD If an iBOR of iSD is not determined, Step 4 will be performed.	At least one iSD assessment (or better), ≥ 6 weeks (≥ 42 days) after baseline; if not, at least one follow-up scan (i.e., consecutive scan) evaluated as iSD (or better) is required to determine an iBOR of iSD. If not consecutive scans, with no other assessment between the two determinations other than NE, iCR, iPR, iSD.
Step 4: iBOR of iCPD	At least one (i.e., any) iCPD after baseline.

If an iBOR of iCPD is not determined, Step 5 will be performed.	
Step 5: iBOR of iUPD If an iBOR of iUPD is not determined, Step 6 will be performed.	At least one (i.e., any) iUPD after baseline.
Step 6: iBOR of NE	Measurable disease at baseline, but not all or any target lesions have been evaluated, or if derivation of iBOR from Step 1 to 6 does not apply. Non-measurable disease at baseline will also result in iBOR of NE

The best overall response will be determined for all protocol specified assessments, i.e. scheduled assessments and also for all unscheduled assessments with non-missing information.

Confirmatory scanning (Table 3) for patients who have obtained PR or CR (or respectively iPR or iCR) is needed and should be approximately 4 weeks after the initial response.

Table 3 Confirmation CR and PR

Response: First Time Point	Subsequent Time Point	BOR
CR	CR	CR
CR	PR	SD, PD or PR (see comment*)
CR	SD	SD provided minimum criteria for SD duration met#, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met#, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met#, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met#, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met#, otherwise NE
NE	NE	NE

* Sometimes (i)CR may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had (i)PR, not (i)CR at the first time point. Under these circumstances, the original (i)CR should be changed to (i)PR in the eCRF and the best response is (i)PR. If that is not the case, the (i)BOR of (i)SD will be determined considering two consecutive assessments better than (i)SD. This applies to both RECIST 1.1 and iRECIST..
# At least one SD assessment (or better), ≥ 6 weeks (≥ 42 days) after baseline; if not, at least one follow-up scan (i.e., consecutive scan) evaluated as SD (or better) is required to determine a BOR of SD. If not consecutive scans, with no other assessment between the two determinations other than NE, CR, PR, SD..

5.5.3.2. iORR

The iORR is defined as the proportion of patients with iCR or iPR. iORR will be analyzed in the efficacy population and presented as a point estimate along with 95% Clopper-Pearson CI. Patients with missing data will be considered as non-responders.

iORR analysis will be repeated for ASaT and PP populations and will be repeated in the efficacy population where patients with missing data will be excluded from the analysis.

ORR according to iRECIST will also be listed for the enrolled population.

5.5.3.3. DoR and iDoR

The DoR and iDoR are defined as the time until progression of disease or death for patients with PR, iPR or CR, iCR and will be summarized using Kaplan-Meier estimates in the efficacy population. Responders will be considered to have an ongoing response if they:

- have not progressed, and
- have not started a next-line anti-cancer therapy, and
- have not been lost to follow-up, and
- are alive.

Patients with missing data will be censored/considered as having an event as specified in the table below.

Table 4 DoR and iDoR events and censoring

Situation	Date of progression or censoring	Outcome
No progression, no death. No start of next-line anti-cancer therapy.	Date of the last evaluable tumor assessment.	Censored
No progression, no death. Start of next-line anti-cancer therapy.	Date of the last tumor assessment with non-progression before the start of next-line anti-cancer therapy.	Censored
Progression or death after one missed adequate tumor assessment.	Date of progression or death, whichever is earliest (if both occur).	Progressed
Progression or death after more than one missed adequate tumor assessment.	Date of the last evaluable tumor assessment.	Censored

For DOR, the start date is the date of first documented response of CR or PR (i.e. the start date of response, not the date when response was confirmed), and the end date is defined as the date of the first documented progression or death.

For iDOR, the start date is the date of first documented response of iCR or iPR (i.e. the start date of response, not the date when response was confirmed), and the end date is defined as the date of the first documented progression according to iRECIST or death.

The progression date to be used for calculation of iDOR should be the first date at which progression criteria are met (i.e, the date of iUPD) provided that iCPD is confirmed at the

next assessment. If iUPD occurs, but is disregarded because of later iSD, iPR, or iCR, that iUPD date should not be used as the progression event date.

If progression is not confirmed and there is no subsequent iSD, iPR, or iCR, the iUPD date should still be used if:

- the patient stops protocol treatment because they were not judged to be clinically stable, or
- no further tumor assessments are done, or
- the next timepoint responses are all iUPD, and iCPD never occurs, or
- the patient dies from his cancer.

DOR according to RECIST and iRECIST will be presented in a data listing for ASaT population.

DOR according to RECIST and iRECIST will be presented graphically using Kaplan-meier plots for efficacy and ASaT populations including count for numbers of patients at risk.

5.5.3.4. CBR and iCBR

The CBR and iCBR are defined as the number of PR, iPR, CR, iCR, and SD, iSD and will be analyzed in the efficacy population and presented as a point estimate along with 95% Clopper-Pearson CI. SD, iSD needs to last at least 6 weeks from the start of study treatment; if not, at least one follow-up scan is required to declare stable disease. Patients with missing data will be considered as non-responders.

The analysis will be repeated for ASaT and PP populations as well as in the efficacy population where patients with missing data will be excluded from the analysis.

CBR according to RECIST and iRECIST will be presented in a data listing for ASaT population.

5.5.3.5. PFS and iPFS

PFS and iPFS are defined as the time from the first day of study treatment until the first date of radiological disease progression or death and will be summarized using Kaplan-Meier estimates in the efficacy population.

Patients with missing data will be censored/considered as having an event as specified in the table below.

Table 5 PFS and iPFS events and censoring

Situation	Date of progression or censoring	Outcome
Incomplete or no baseline tumor assessment.	First day of study treatment	Censored

Start of next-line anti-cancer therapy.	Date of the last tumor assessment with non-progression before the start of next-line anti-cancer therapy.	Censored
Death before the first disease progression assessment.	Date of death.	Progressed
Death between adequate tumor assessment visits.	Date of death.	Progressed
Progression or death after one missed adequate tumor assessment.	Date of progression or death, whichever is earliest (if both occur).	Progressed
Progression or death after more than one missed adequate tumor assessment.	Date of the last evaluable tumor assessment.	Censored
No progression, no death.	Date of the last evaluable tumor assessment.	Censored

For iPFS, the progression date to be used for calculation should be the first date at which progression criteria are met (i.e, the date of iUPD) provided that iCPD is confirmed at the next assessment. If iUPD occurs, but is disregarded because of later iSD, iPR, or iCR, that iUPD date should not be used as the progression event date.

If progression is not confirmed and there is no subsequent iSD, iPR, or iCR, the iUPD date should still be used if:

- the patient stops protocol treatment because they were not judged to be clinically stable, or
- no further tumor assessments are done, or
- the next timepoint responses are all iUPD, and iCPD never occurs, or
- the patient dies from his cancer.

PFS according to RECIST and iRECIST will be listed for ASaT population.

PFS according to RECIST and iRECIST will be displayed graphically using Kaplan-meier plots for efficacy and ASaT populations including count for numbers of patients at risk.

5.5.3.6. TtR and iTtR

TtR and iTtR are defined as the time from the first day of study treatment until the first date of PR, iPR or CR, iCR and will be summarized using Kaplan-Meier estimates in the efficacy population.

Confirmed response dates will be used. Patients with missing data will be censored at the last assessment date, date of death, or date of eligibility (if incomplete or no baseline tumor assessments), whichever occurs latest.

TTR according to RECIST and iRECIST will be listed for ASaT population.

TTR according to RECIST and iRECIST will be displayed graphically using Kaplan-meier plots for efficacy and ASaT populations including count for numbers of patients at risk.

5.5.3.7. TtP and iTtP

TtP and iTtP are defined as the time from the first day of study treatment until the first date of radiological disease progression and will be summarized using Kaplan-Meier estimates in the efficacy population.

Patients with missing data will be censored/considered as having an event as specified in Table below.

Table 6 TtP and iTtP events and censoring

Situation	Date of progression or censoring	Outcome
Incomplete or no baseline tumor assessment.	First day of study treatment	Censored
Start of next-line anti-cancer therapy.	Date of the last tumor assessment with non-progression before the start of next-line anti-cancer therapy.	Censored
Death before the first disease progression assessment.	Date of death.	Censored
Death between adequate tumor assessment visits.	Date of death.	Censored
Death after one missed adequate tumor assessment.	Date of death.	Censored
Progression after one missed adequate tumor assessment.	Date of progression.	Progressed
Progression after more than one missed adequate tumor assessment.	Date of the last evaluable tumor assessment.	Censored
No progression.	Date of the last evaluable tumor assessment.	Censored

For iTtP, the progression date to be used for calculation should be the first date at which progression criteria are met (i.e, the date of iUPD) provided that iCPD is confirmed at the next assessment. If iUPD occurs, but is disregarded because of later iSD, iPR, or iCR, that iUPD date should not be used as the progression event date.

If progression is not confirmed and there is no subsequent iSD, iPR, or iCR, the iUPD date should still be used if:

- the patient stops protocol treatment because they were not judged to be clinically stable, or
- no further tumor assessments are done, or
- the next timepoint responses are all iUPD, and iCPD never occurs, or
- the patient dies from his cancer.

TtP according to RECIST and iRECIST will be listed for ASaT population.

TtP according to RECIST and iRECIST will be displayed graphically using Kaplan-meier plots for efficacy and ASaT populations including count for numbers of patients at risk.

5.5.4. Sensitivity Analyses for the Secondary Efficacy Analysis

Secondary efficacy analysis will be repeated for ASaT population.

5.5.5. Subgroup Analysis

Not Applicable

5.5.6. Exploratory Analysis

5.5.6.1. PFS2

PFS2 is defined as the time from the first day of study treatment until the date of second disease progression (i.e., progression on next-line anti-cancer treatment) or death and will be summarized using Kaplan-Meier estimates in the ASaT population. Patients with missing data (i.e., without second radiological disease progression) will be censored at the last time known to be alive.

PFS2 data will be listed for ASaT population.

PFS2 will be presented graphically using Kaplan-Meier plots for ASaT population.

5.5.6.2. OS

OS is defined as the time from the first day of study treatment until the date of death and will be summarized using Kaplan-Meier estimates in the ASaT population.

Patients with missing data will be censored at the last date known to be alive. The last known date to be alive will be derived for patients at the analysis cutoff using the latest complete date among the following:

- Patient assessment dates (blood draws [laboratory, PK], vital signs, ECOG performance status, ECG, tumor assessments, tumor measurement, or tumor biopsy dates)
- Start and end dates of anti-cancer therapies administered after study treatment discontinuation
- AE start and end dates
- Concomitant medication start and end dates
- Concurrent procedure date
- Date of death collected on the 'Death Details' electronic Case Report Form (eCRF)
- Date of last contact collected on the 'Survival Status' eCRF where status is 'alive'; or date last known to be alive if status is 'unknown'
- Study treatment start and end dates
- Date of discontinuation on disposition eCRF pages (do not use if reason for discontinuation is lost to follow-up).

Only dates associated with actual contact of the patient will be used in the derivation. Dates associated with a technical operation unrelated to patient status such as the date a blood sample was processed will not be used. Assessment dates after the cutoff date will not be applied to derive the last contact date, if applicable.

OS data will be listed for ASaT population.

OS will be presented graphically using Kaplan-Meier plots ASaT population.

5.5.6.3. Duration of Follow up

A reverse Kaplan-Meier analysis will be performed on OS in the ASaT population to estimate the median follow-up incorporating censoring rules and flipping event/censored events.

Duration of Follow up data will be listed for ASaT population.

Duration of Follow up will be presented graphically using Kaplan-Meier plots ASaT population.

5.5.6.4. Assessment of the EGFR mutational status at baseline and at disease progression

EGFR mutational status will be listed for ASaT population.

5.5.6.5. Tumor Burden Analysis

Absolute change from baseline and percent change from baseline for sum of target and new lesion diameters will be summarized in the efficacy population using descriptive statistics for each week of tumor assessment. The best percent change of sum of target and new target lesion will be presented in summary tables.

A waterfall plot of maximum percent reduction in the sum of diameter of target lesions from baseline will be created in the efficacy population. These plots will display the best percentage CFB in the sum of the diameter of all target lesions for each patient.

A spaghetti plot of percent reduction in the sum of target lesions from baseline will be created in the efficacy population to plot the change in tumor burden over time (in weeks from start of treatment) for each patient.

Best percent change from baseline for sum of target lesion diameters is defined as the lowest (minimum) percent change from baseline and will be calculated with one decimal place.

Sum of target lesion diameters will be listed for enrolled population.

5.6. Safety

5.6.1. Extent of Exposure and Compliance

Exposure/Compliance	nanrilkefusp alfa	Cetuximab
Cycle Started	Patient received at least one dose of nanrilkefusp alfa in that cycle	Patient received at least one dose of cetuximab in that cycle
	Cycle started in combination therapy is defined as patient receiving at least one dose of nanrilkefusp alfa and cetuximab in that cycle.	
Completed cycle	Patient received 4 doses of nanrilkefusp alfa and 3 doses of cetuximab in that cycle, or patient started the next cycle.	
Duration of cycle (days)	The day prior to the date of cycle start (day 1 in each cycle) will be considered as the end of the previous cycle. For the last cycle, 21 days will be used.	
Duration of exposure (days)	Last dose date – Start dose date + 1	Last dose date – Start dose date + 1
	Last dose date of either nanrilkefusp alfa or cetuximab, whichever is later – Start dose date of nanrilkefusp alfa or cetuximab, whichever is earlier + 1	
Real dose administered	(2 x Total volume administered) / patient weight (µg/kg)	Actual dose per administration / BSA (mg/m²)
Actual cumulative dose	Sum of the real doses (µg/kg) administered	Sum of the real doses (mg/m²) administered
Duration of exposure (days) for completed cycles (*)	Considering only completed cycles: End date of last completed cycle – Start dose date of nanrilkefusp alfa or cetuximab, whichever is earlier + 1	

Exposure/Compliance	nanrilkefusp alfa	Cetuximab
Actual dose intensity (*)	Considering only completed cycles: Actual cumulative dose / Duration of exposure for completed cycles (days) in (µg/kg/day)	Considering only completed cycles: Actual cumulative dose / Duration of exposure for completed cycles (days) in (mg/m²/day)
Actual dose intensity by cycle (*)	Considering only completed cycles: Actual cumulative dose in that cycle / Duration of cycle (days) in (µg/kg/day)	Considering only completed cycles: Actual cumulative dose in that cycle / Duration of cycle (days) in (mg/m²/day)
Intended dose intensity	(Initial dose of nanrilkefusp alfa * 4 doses)/ 21 day	(As per protocol initial dosing)/ 21 day Protocol initial dosing : 900 mg/m² of BSA for cycle 1 750 mg/m² of BSA for subsequent cycles
Relative dose intensity by cycle (%) (*)	Considering only completed cycles: 100 * (Actual dose intensity by cycle / Intended dose intensity)	Considering only completed cycles: 100 * (Actual dose intensity by cycle / Intended dose intensity)
Overall relative dose intensity (%) (*)	Considering only completed cycles: 100 * (Actual dose intensity / Intended dose intensity)	Considering only completed cycles: 100 * (Actual dose intensity / Intended dose intensity)
Compliance with planned dose (%)	100 * (Real dose administered / Planned dose) at each dosing, taking into account per protocol dose changes	100 * (Real dose administered / Planned dose) at each dosing, taking into account per protocol dose changes

(*) only completed cycle as defined should be considered for derivation.

Descriptive statistics in the ASaT population and Efficacy population will be provided for:

- Total number of cycles started
- Total number of doses administered as well as the frequency of patients with 1, 2, 3, 4, 5, 6, 7, 8, or ≥9 injections.
- Duration of exposure
- Number of patients with at least one dose adjustment
- Actual cumulative dose
- Actual dose intensity
- Overall relative dose intensity

For the combination therapy, the total number of cycles started and the duration of exposure will be summarized.

Treatment compliance will be listed together with exposure for the ASaT population. Missing data will not be imputed and only original data for those fields (for example, date fields) will be presented in the listing together with derived variables such as the calculated compliance (%) and exposure duration.

Further, study treatment administration/infusion data (including total volume administered and dose adjustments, etc.) will be listed for the ASaT population.

Mean of Relative Dose Intensity by Cycle will be presented graphically for ASaT population using bar chart.

5.6.2. Dose Limiting Toxicities

DLT evaluability is defined for patients in Safety cohorts as follows:

- Patient completed the first 21-day cycle (DLT assessment period of 21 days)
- Patient received all administrations of nanrilkefusp alfa during the DLT period as per schedule (±1 day)
- Patient received cetuximab as per schedule (±1 day)
- Patients experienced at least one DLT during the DLT assessment period, regardless of the number of nanrilkefusp alfa or cetuximab administrations during the DLT period

DLTs will be identified in the Adverse event eCRF page with “Is the adverse event a Dose Limiting Toxicity?” =” Yes”.

Patient needs to receive all administrations of nanrilkefusp alfa and cetuximab during the DLT period as planned per schedule.

The incidence of DLTs by dose level will be summarized with counts and percentages by SOC and PT in ASaT population.

A listing of all DLTs including the first and last dates of treatment will be presented for the ASaT population.

5.6.3. **Adverse Events**

All AEs recorded on the eCRF will be coded using the MedDRA dictionary [most recent version at time of DB lock] and classified as either pre-treatment AEs or treatment–emergent AEs (TEAEs) as follows:

- CRS symptoms will not be considered in the analysis to avoid duplication, as the diagnosis is reported instead.
- Pre-treatment AEs are events that start prior to the start of the study treatment.
- A TEAE is defined as an AE that started or worsened at or after the start of study treatment.
- Treatment-Emergent Serious AEs (TESAEs) will be defined as TEAEs deemed by the investigator as Serious = "Yes".
- The relationship between a TEAE and nanrilkefusp alfa treatment is assessed as suspected or not suspected (same with cetuximab). A nanrilkefusp alfa treatment-related TEAE will be defined as a TEAE considered by the investigator as suspected. A cetuximab-related TEAE will be defined as a TEAE considered by the investigator as suspected.
- Assessment of AE severity/intensity will be based on the NCI-CTCAE (version 5.0). Severe TEAEs are defined as TEAEs assessed as being "Severe (=Grade 3)/ Grade 4/Grade 5" in intensity.
- TEAEs leading to dose reduction of nanrilkefusp alfa treatment are defined as TEAEs where "Dose reduced" is indicated as "Yes".
- TEAEs leading to temporary discontinuation of nanrilkefusp alfa treatment are defined as TEAEs where "Temporarily discontinued" is indicated as "Yes".
- TEAEs leading to permanent discontinuation of nanrilkefusp alfa treatment are defined as TEAEs where "Permanently discontinued" is indicated as "Yes".
- TEAEs leading to dose reduction of cetuximab treatment are defined as TEAEs where "Dose reduced" is indicated as "Yes".
- TEAEs leading to temporary discontinuation of cetuximab treatment are defined as TEAEs where "Temporarily discontinued" is indicated as "Yes".
- TEAEs leading to permanent discontinuation of cetuximab treatment are defined as TEAEs where "Permanently discontinued" is indicated as "Yes".

According to the eCRF, if a patient has (for example) 2 episodes of a same AE but a change in intensity, they will be identified using the 2 following CRF items:

- Is this a change in severity of an already existing AE equals to "Yes"
- If Yes, AE identifier.

In that case, to derive the TEAE flag, the AE identified/linked with the items above will be considered as the same "linked" AE but with 2 episodes. Thus, if worsening or both TEAE, the linked AE (both episodes) will be flagged as the TEAE.

Linked AEs will be selected for analysis in tables based on their worst case scenario attribute e.g. maximum CTC grade, causal relationship, seriousness, treatment emergence and action taken out of all records.

The ordering (the worst to best) for the following characteristics will be applied:

- Action taken: permanently discontinued, temporarily discontinued, dose reduced, other action, no action taken.
- Relationship: suspected, not suspected.
- Toxicity Grade: Grade 5 to Grade 1.

AE records within a linked AE can be given different treatment-emergence status. Treatment emergence for linked AEs will be established as those records in the linked AE with a worsening of severity from the preceding record.

Adverse events will be summarized by default descriptive summary statistics for categorical variables for the ASaT population by overall as follows:

Combination treatment related is defined as being related to either nanrilkefusp alfa or cetuximab (or both), and discontinuation of combination treatment means discontinuation of either nanrilkefusp alfa or cetuximab (or both).

- An overview of TEAEs including the number and percentage of patients with at least one of each mentioned TEAE type:
    - Any TEAE
        - Leading to dose reduction of nanrilkefusp alfa
        - Leading to temporary discontinuation of nanrilkefusp alfa
        - Leading to dose reduction and temporary discontinuation of nanrilkefusp alfa.
        - Leading to permanent discontinuation of nanrilkefusp alfa
        - Leading to permanent discontinuation of combination treatment
        - Serious
        - Grade 1 severity (mild)
        - Grade 2 severity (moderate)
        - Grade 3 severity (severe)
        - Grade 4 severity (life-threatening or disabling)
        - Grade 5 severity (death related to TEAE)
        - ≥Grade 3 severity (severe, life-threatening, disabling, death related to TEAE)
    - Any nanrilkefusp alfa-related TEAE
        - Leading to permanent discontinuation of nanrilkefusp alfa
        - Leading to permanent discontinuation of combination treatment.
        - Serious

        - Grade 1 severity (mild)
        - Grade 2 severity (moderate)
        - Grade 3 severity (severe)
        - Grade 4 severity (life-threatening or disabling)
        - Grade 5 severity (death related to TEAE)
        - ≥Grade 3 severity (severe, life-threatening, disabling, death related to TEAE)
    - Any combination-related TEAE
        - Leading to permanent discontinuation of combination treatment
        - Serious
        - Grade 1 severity (mild)
        - Grade 2 severity (moderate)
        - Grade 3 severity (severe)
        - Grade 4 severity (life-threatening or disabling)
        - Grade 5 severity (death related to TEAE)
        - ≥Grade 3 severity (severe, life-threatening, disabling, death related to TEAE)
- The number and percentage of patients reporting each TEAE and the count of number of events will be summarized by SOC and PT for the following types of TEAEs in the ASaT population:
    - TEAEs
    - TEAEs occurring in ≥ 5% of patients
    - TEAEs leading to dose reduction of nanrilkefusp alfa
    - TEAEs leading to temporary discontinuation of nanrilkefusp alfa
    - TEAEs leading to dose reduction and temporary discontinuation of nanrilkefusp alfa
    - TEAEs leading to permanent discontinuation of nanrilkefusp alfa
    - TEAEs leading to temporary discontinuation of cetuximab
    - TEAEs leading to permanent discontinuation of cetuximab
    - TEAEs leading to permanent discontinuation of combination treatment
    - TEAEs leading to death
    - Serious TEAEs
    - Non-serious TEAEs occurring in ≥5% of patients
    - TEAEs with ≥ Grade 3 severity
    - TEAEs with ≥ Grade 3 severity occurring in ≥ 5% of patients
    - TEAEs by maximum severity grade
    - nanrilkefusp alfa-related TEAEs
    - nanrilkefusp alfa-related TEAEs leading to permanent discontinuation of nanrilkefusp alfa
    - nanrilkefusp alfa-related TEAEs leading to death
    - Serious nanrilkefusp alfa-related TEAEs
    - nanrilkefusp alfa-related TEAEs with ≥ Grade 3 severity
    - nanrilkefusp alfa-related TEAEs by maximum severity grade

  - Combination-treatment-related TEAEs
  - Combination-treatment-related TEAEs leading to death
  - Serious combination-treatment-related TEAEs
  - Combination-treatment-related TEAEs with ≥ Grade 3 severity
  - Combination-treatment-related TEAEs by maximum severity grade

- The number and percentage of patients reporting each TEAE and the count of number of events will be summarized by PT for the following types of TEAEs:
  - TEAEs
  - TEAEs occurring in ≥5% of patients
  - nanrilkefusp alfa-related TEAEs
  - Combination-treatment-related TEAEs
  - Serious TEAEs
  - Serious nanrilkefusp alfa-related TEAEs
  - Serious combination-treatment-related TEAEs
- The number and percentage of patients who died will be summarized by the primary and secondary reason of death in the enrolled population.

In the above summaries, patients with more than one TEAE within a particular SOC are counted only once for that SOC. Similarly, patients with more than one TEAE within a particular PT are counted only once for that PT.

For summaries by maximum severity, patients with multiple TEAEs within a particular SOC or PT will be counted under the category of their most severe TEAE within that SOC or PT.

Summaries by SOCs and PTs will be sorted by SOCs by their descending Order (MedDRA) and PTs within SOC by descending order of total incidence. Where preferred terms tie PTs will be sorted alphabetically.

All AE data will be listed and Pre-treatment AEs and TEAEs will be presented together. Treatment-emergence status will be flagged in the listing. The listing will present the relative start and stop day of the AE calculated relative to the first dose of treatment and will be presented for those patients who received at least one dose of treatment. If the AE is "Ongoing" it will be indicated as such in the listing and the relative stop day will not be calculated. Only original dates will be presented in the listing even though the relative day may be based on an imputed date.

In addition, the following listings will be presented:

- Listing of deaths
- Listing of AEs
- Listing of serious TEAEs
- Listing of TEAEs leading to temporary discontinuation of nanrilkefusp alfa

- Listing of TEAEs leading to dose reduction of nanrilkefusp alfa
- Listing of TEAEs leading to permanent discontinuation of cetuximab

TEAE occurring in >= 10% of patients will be presented graphically for ASaT population.

5.6.4. **Laboratory Evaluat**ions

Data for the following coagulation, hematology, and biochemistry analytes received from local laboratory are to be measured at the scheduled visits indicated in the study flowchart.

All parameters recorded in the study will be included in the listings, but only parameters defined in

Table 7 specifies the tests that will be included in the summaries.

Table 7 Laboratory Tests to Be Included in Summaries

Hematology Test (SI unit)	Biochemistry Test (SI unit)	Coagulation
○ Hemoglobin (g/L) ○ Differential WBC (10^9/L and %) • Neutrophils • Lymphocytes ○ Absolute lymphocyte count ○ Platelet count (10^9/L)	○ Alanine aminotransferase (ALT) (U/L) ○ Aspartate aminotransferase (AST) (U/L) ○ Total Bilirubin (mmol/L) ○ Lactate Dehydrogenase ○ Alkaline phosphatase (U/L) ○ C-reactive protein ○ Albumin (g/L) ○ Creatinine (mmol/L) ○ Creatinine Clearance (mL/s)	○ D-dimer

All laboratory data will be reported in SI units. All quantitative laboratory test values at each assessed visit will be compared with the relevant reference range in SI units and categorized as:

Low: Below the lower limit of the reference range.

Normal: Within the reference range (upper and lower limits included).

High: Above the upper limit of the reference range.

For analysis purposes, values preceded by a "<" or a ">" sign (i.e. those below or above the limits of quantification) will be considered equal to the lower or upper limit of quantification, respectively.

Laboratory data will be summarized by default descriptive summary statistics for continuous and categorical variables for the ASaT population by overall as follows:

- Observed values and change from baseline at each scheduled assessed visit for each standard continuous laboratory parameter

Listings of all clinical laboratory data including derived change from baseline will be provided for the screened population. Within each listing, laboratory values outside the normal ranges will be flagged as either high or low for applicable laboratory assessments.

Hematology, Coagulation and Biochemistry results for selected laboratory parameters for each scheduled visit will be displayed graphically using boxplots showing the summary data per scheduled assessment, including an overlaid mean profile line and approximate lower limit of normal reference range (LLN) and upper limit of normal reference range (ULN) reference lines indicated by overall for ASaT population.

5.6.5. Hy's Law for Liver Function Tests

Hepatic function abnormality defined by an increase in AST and/or ALT to ≥3xULN concurrent with an increase in total bilirubin to ≥2xULN but without increase in alkaline phosphatase (i.e., alkaline phosphatase <2xULN) meets the criteria for Hy's law and raises the concern for drug-induced liver injury when no other cause is identified.

The summary of liver function tests will include the following categories, and the number and percentage of patients meeting Hy's Law at each scheduled visit during the on-treatment period will be summarized for ASaT population.

An eDISH figure displaying patients who reach 3xULN for ALT or AST, plus 2xULN for total bilirubin and thus are at risk for a drug induced liver injury according to Hy's law will be presented for ASaT population. A listing of patients at risk will also be presented for screened population.

5.6.6. **Vital Signs**

The analyses described below will be conducted for the following vital signs assessments respectively:

- SBP (mmHg);
- DBP (mmHg);
- Heart rate (bpm);
- Body Temperature (°C)

The following will be summarized by overall for the ASaT population:

- Observed values and change from baseline at each scheduled assessed visit for each standard vital sign parameter using default summary statistics for continuous variables

A listing of all vital signs data including derived change from baseline will be provided for the screened population.

The actual values and CFB for each scheduled study visit for selected vital signs parameters will be plotted at each time point using a line plot including 95% CI bars around the mean, this will be done by overall for ASaT population.

Total counts and percentages of patients will be presented for the following:

- Maximum increase from baseline in SBP and DBP (mmHg):
  - <20
  - >=20 and <40
  - >=40 and <60
  - >=60
- Maximum decrease from baseline in SBP and DBP (mmHg):
  - <20
  - >=20 and <40
  - >=40 and <60
  - >=60
- Maximum increase from baseline in heart rate (bmp):
  - <30
  - >=30
- Maximum decrease from baseline in heart rate (bmp):
  - <30
  - >=30
- Maximum postdose heart rate (bmp)
  - <50
  - >=50 and <120
  - >=120

5.6.7. **Body Surface Area**

The analyses described below will be conducted for the following BSA assessments respectively:

- Height (cm);
- Weight (kg);
- Body Surface Area (m^2)

A listing of all body surface area data including derived change from baseline will be provided for the screened population.

5.6.8. Electrocardiograms

The following ECG assessments will be taken during the study:

- An overall investigator assessment classified as normal / abnormal, not clinically significant / abnormal, clinically significant / unevaluable / unknown
- Heart rate (bpm);
- PR interval (msec);
- QRS interval (msec);
- QT interval (msec);

- Bazett Corrected QT (QTcB) interval (msec);
- Fridericia Corrected QT (QTcF) interval (msec)

A listing of all ECG data will be provided for the screened population.

5.6.9. Left Ventricular Ejection Fraction (LVEF)

LVEF data will be listed for ASaT population.

5.6.10. Physical Examination

Physical examination data will be listed for each patient at each assessed visit for the screened population.

5.6.11. Other Safety Variables

5.6.11.1. Eastern Cooperative Oncology Group (ECOG)

Total counts and percentages of patients will be presented for the ECOG performance status scores on the ASaT population.

ECOG performance status scores will be listed for each patient at each assessed visit for the ASaT population.

5.6.11.2. Pregnancy Test

Pregnancy test results will be listed for each patient at each assessed visit for the screened population.

5.6.12. Interim Analysis and Data Monitoring

An analysis for futility will be performed when the sample size is considered enough for such analysis. Efficacy data and outputs will also be a part of the IDMC review.

The futility analysis will be conducted once all patients in the efficacy population planned for futility analysis will have post-baseline tumor assessment data or discontinue the treatment before the post-baseline assessment. Patients in efficacy population who discontinue and have no evaluable post-baseline tumor assessment available will be considered as non-responders.

Assuming a desired ORR, the futility analysis will be based on a comparison against a minimal ORR considered as both statistically and clinically relevant improvement as compared to the benchmark ORR. An 80% CI using the exact method for the ORR (alpha = 0.2, alpha = 0.1 one-sided) will be used. The analysis will be based on the efficacy population.

If the ORR is:

- lower than the minimal ORR, and
- the 80% CI for the ORR does not include the minimal ORR,

It will be concluded that the combination treatment is futile as compared to cetuximab treatment alone and thus the study will be discontinued. However, patients still on treatment can continue combination therapy if recommended by the IDMC.

The criteria for conclusion of futility are defined as follows:

- Benchmark ORR = 20%; minimal ORR = 28.8%; desired ORR = 36.8%
- N = 16 patients if the number of responses is less than 2 (r <2)

Additionally, the ORR will be evaluated on an ongoing basis (without stopping of recruitment). Other efficacy endpoints will be used as supportive information.

For the purposes of interim analyses, in the case of ongoing patients with any unconfirmed response and for whom a confirmatory scan is still pending:

- Responders (PR, CR) or patients with SD that, at the time of the futility analysis, did not yet have a second (confirmatory) tumor assessment performed will be considered to have an Unconfirmed response (PR, CR) or Unconfirmed SD as BOR, respectively. Such BORs will be presented with "Unconfirmed" label.
- ORR will also include Unconfirmed PR and Unconfirmed CR in the numerator.

5.7. Pharmacokinetic Analysis

The serum concentrations will be evaluated for nanrilkefusp alfa analyte and may or may not be evaluated for the cetuximab analyte (cetuximab samples will be collected to be analyzed later during the course of the study, if needed). Serum samples will be collected from all patients in the initial safety cohorts and from the first 12 patients in the main study cohort. The actual date and time (24-hour clock time) of each serum sample will be recorded.

The following PK parameters will be determined where possible from the serum concentrations of nanrilkefusp alfa using non-compartmental methods in the validated software program Phoenix WinNonlin (Certara, Version 8.3.5 or higher):

Parameter	Definition
AUC_{last}	area under the concentration-time curve over the last measurable concentration (T_{last}) (Cycle 1 Day 1 only)
$AUC_{(0-4h)}$	area under the concentration-time curve over time 0 to 4 hours postdose (Cycle 1 Day 1 only)
$AUC_{(0-24h)}$	area under the concentration-time curve over time 0 to 24 hours postdose (Cycle 1 Day 1 only)
C_{max}	observed maximum concentration (Cycle 1 Day 1 only)
C_{2h}	observed concentration at 2 hours postdose (Cycle 1 and 3 Days 1)

Parameter	Definition
C_{trough}	observed trough concentration (Cycle 1 Day 2 predose = Cycle 1 Day 1 trough; Cycle 1 Day 9 predose = Cycle 1 Day 8 trough; Cycle 3 Day 1 predose = Cycle 2 Day 9 trough)
T_{max}	time to maximum concentration (Cycle 1 Day 1 only)
T_{last}	time of the last measurable concentration (Cycle 1 Day 1 only)
$R_{C2h,}$ and $R_{Ctrough}$	Accumulation Ratio of C_{2h} on Cycle 3 Day 1/Cycle 1 Day 1 Accumulation Ratio of Ctrough on Cycle 2 Day 9/Cycle 1 Day 1

For the Cycle 1 Day 1 profile, the Cycle 1 Day 2 predose concentration will be the 24 hour timepoint.

If cetuximab concentrations are available, C_{trough} will be reported for Cycle 1 (predose concentration on Day 8 and 15) and Cycle 3 (predose concentration on Day 1).

Additional PK parameters may be determined where appropriate.

The units of the PK parameters will be based on the concentration units provided by the bioanalytical laboratory and the dose units used in the study.

Pharmacokinetic analysis will be carried out where possible using actual dose administered (µg for nanrilkefusp alfa) and actual postdose blood sampling times. If an actual time is missing, the sample concentration result will be treated as missing unless there is scientific justification to include the result using the nominal time.

The parameters C_{max}, C_{trough}, C_{2h}, T_{last}, and T_{max} will be obtained directly from the concentration-time profiles. If C_{max} occurs at more than 1 timepoint, T_{max} will be assigned to the first occurrence of C_{max}.

The area under the concentration-time curve (AUC) parameters will be calculated using the linear trapezoidal rule for increasing concentrations and the logarithmic rule for decreasing concentrations (linear up/log down rule).

5.7.1. Criteria for Calculation and Reporting of Area Under the Concentration-time Curve

The minimum requirement for the calculation of AUC will be the inclusion of at least 3 consecutive concentrations above the lower limit of quantification. If there are only 3 consecutive concentrations, at least 1 should follow C_{max}.

For calculation of the partial AUC parameters, if the end interval PK sample is collected slightly earlier than the nominal time, the AUC parameter will be calculated using the end interval sample if the collection is within ± 10% of the nominal sampling time.

5.7.2. Criteria for Handling Concentrations Below the Limit of Quantification or Missing Concentrations for Pharmacokinetic Analysis

Serum concentrations below the limit of quantification (BLQ) will be assigned a value of 0 before the first measurable concentration and thereafter BLQ concentrations will be treated as missing. The following rules apply to the specific situations defined below:

- If an entire concentration-time profile is BLQ, it will be excluded from PK analysis.
- Where 2 or more consecutive concentrations are BLQ at the end of a concentration-time curve, the curve will be deemed to have terminated and any further quantifiable concentrations will be set to missing for the calculation of the PK parameters, unless they are considered to be a true characteristic of the profile of the drug.
- If a predose serum concentration is missing on the first day of dosing day (Cycle 1 Day 1), it will be set to 0 by default within Phoenix WinNonlin.

5.7.3. Treatment of Outliers in Pharmacokinetic Analysis

If a value is considered to be anomalous due to being inconsistent with the expected PK profile, it may be appropriate to exclude the value from the PK analysis. However, the exclusion of any data must have strong justification and will be documented in data review meeting minutes.

Any quantifiable predose concentration value on the first day of dosing (Cycle 1 Day 1) will be considered anomalous and set to missing which Phoenix WinNonlin will apply as 0 by default for the PK analysis.

5.7.4. Presentation of Pharmacokinetic Data

A listing of PK blood sample collection times and serum concentrations will be presented for evaluated analyte(s) separately for all patients for the ASaT Population.

PK concentrations will be summarized for the PK Population by analyte, cycle, profile day, treatment, and protocol scheduled times using appropriate summary statistics. See Section 4.2.8 for the handling of serum concentrations that are BLQ and the summary statistics to be presented.

Individual concentrations deemed to be anomalous will be flagged in the listings and excluded from the summary statistics. Individual and summary concentration-time figures will be

presented on both linear and semi-logarithmic scales. PK concentrations by analyte, cycle, profile day, treatment, and nominal time postdose will be displayed for the PK Population using arithmetic mean (+ SD) figures and median figures. Overlaying individual figures and individual figures will be displayed using actual time postdose. For all individual and summary concentration-time figures: Cycle 1 Day 2 predose will be set as the 24 hour postdose concentration for the Cycle 1 Day 1 profile for nanrilkefusp alfa; the Cycle 1 Day 8 predose will be set as the 168 hour postdose concentration for the Cycle 1 Day 1 profile for cetuximab.

A listing of PK parameters will be presented for evaluated analyte(s) separately for all patients in the PK Population.

PK parameters will be summarized for the PK Population by analyte, cycle, profile day, and treatment using the summary statistics: geometric mean, CV% (inter-patient), arithmetic mean, SD, median, minimum, maximum, number of patients with data available (n), and number of patients in analysis set (N), with the exception of T_{max} and T_{last} where only N, n, minimum, median and maximum will be presented. PK parameter summary statistics will be calculated only if there are at least 3 evaluable data ($n \geq 3$) available, otherwise only the N, n, minimum and the maximum are presented and other statistics are shown as not calculated (NC).

5.8. Immunogenicity Assessments

5.8.1. Anti-Drug Antibodies (ADAs) against nanrilkefusp alfa

Samples for ADAs will be collected to assess nanrilkefusp alfa immunogenicity, correlation with PK, and potential AEs associated with ADAs against nanrilkefusp alfa and for the prediction of nanrilkefusp alfa ADA production, including neutralizing ADAs. The correlation assessments will not be reported.

The presence or absence of anti-drug antibodies, neutralizing ADA's and titer categorizations will be summarized by timepoint and actual nanrilkefusp alfa dose level for the ASaT population.

Immunogenicity data will be listed for the screened population.

5.8.2. ADAs against cetuximab

Samples for cetuximab ADAs will be collected. The decision to analyze the samples to assess cetuximab immunogenicity will be taken at a later date and described separately.

5.9. Biomarkers

Biomarker collection data from eCRF will be listed for screened population. Biomarkers results will be reported separately for the CSR.

6. Changes in the Conduct of the Study or Planned Analysis

The following changes or precisions from protocol specified statistical analyses are made in this SAP.

6.1. SD and iSD derivation

SD and iSD needs to last at least 6 weeks from the start of study treatment and not weeks from the baseline scan as it is mentioned in protocol section 9.3.3.1.

6.2. Duration of Follow-Up

Duration of Follow-Up was added as a reverse Kaplan-Meier analysis on OS to estimate the median follow-up incorporating censoring rules and flipping event/censored events.

6.3. PK parameters

Adjusted PK parameters from those listed in the protocol will be derived. The modified PK parameters documented in section 5.7 include only those that are calculable by non-compartmental analysis based on the adjusted PK sampling timepoints in protocol amendment 1.

7. Appendices

Appendix 1: Document History

Document Version, Status, Date	Summary / Reason for Changes
Version 1.0, Final, 19JAN2023	Not applicable; the first version
Version 2.0, Final, 17MAY2023	• Minor updates due to protocol amendment 1 in study objectives • SOT101 updated to nanrilkefusp alfa • Details on the derivation and presentation of PK parameters by non-compartmental analysis are included to reflect the adjusted PK sampling schedule in protocol amendment 1. A separate PK analysis plan is no longer required.
Version 2.0, Final, 17MAY2023	• Name was changed from Labcorp Drug Development to Fortrea

8. References

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