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)

Study interventions	Product code: SOT101 (previously SO-C101, RLI-15); INN: nanrilkefusp alfa Cetuximab
Regulatory agency identifier numbers	EudraCT number: 2022-001527-32 IND number: 140011
Protocol number	SC105 (AURELIO-05)
Phase	2
Version	Protocol Amendment 1
Date	09Mar2023
Sponsor	SOTIO Biotech AG
Legal registered address	Lichtstrasse 35 - WSJ-210 4056 Basel Switzerland

SIGNATURES/PROTOCOL APPROVAL AND RELEASE: SOTIO

We, the undersigned, have read this Protocol and agree that it contains all the necessary information required for the conduct of this clinical trial.

For SOTIO Biotech AG:

[redacted]

Signature: [redacted]

Date: ....……

Signature [redacted]

Date: ....……

[redacted]

SIGNATURES/PROTOCOL APPROVAL AND RELEASE: COORDINATING INVESTIGATOR

I, the undersigned, have read this Protocol and agree that it contains all the necessary information required for the conduct of this clinical trial.

Coordinating investigator:

Signature: ……

Date: ……

INVESTIGATOR'S DECLARATION

I have read this Protocol and I agree that it contains all the necessary details for carrying out this clinical trial. I agree to personally conduct or supervise the clinical trial as described in accordance with the relevant current Protocol and within the time designated. I will only make changes after receiving the sponsor's approval, except when necessary to protect the safety, rights, or welfare of patients.

I verify that I am suitably qualified by education, scientific medical training, and experience to conduct the clinical trial. Documentation of my qualifications and professional affiliations are contained in my up-to-date curriculum vitae.

I will provide the Protocol and all information relating to pre-clinical and previous clinical experience (e.g., Investigator's Brochure) to all associates, colleagues, and staff assisting in the conduct of this clinical trial. I will discuss the material with them to ensure that they are fully conversant with the Protocol, the medical treatment, and the conduct of the clinical trial, and that they will handle the data and information generated in the clinical trial confidentially. I agree to ensure that they are informed about their obligations in meeting the investigator's commitments listed in this Investigator's Declaration, as delegated and applicable to them.

I agree to personally conduct or supervise the clinical trial in accordance with: i) the current version of the Declaration of Helsinki; ii) the current version of International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (ICH E6); iii) the moral, ethical, and scientific principles that justify medical research; and iv) all relevant national and regional laws and regulations relating to clinical trials and the protection of patients of the country in which the clinical trial will be performed.

I will ensure that an institutional review board (IRB) or independent ethics committee (IEC; in the US)/ethics committee (EC; in the EU) that complies with the requirements of national and regional legislation and the Declaration of Helsinki, and that follows the recommendations in ICH E6, will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB/IEC (in the US)/EC (in the EU) all changes in research activity and all unanticipated problems involving risks to patients or others. Additionally, I will not make any changes in the research without IRB/IEC (in the US)/EC (in the EU) approval, except where necessary to eliminate apparent immediate hazards to patients.

I agree to inform all patients and associates, colleagues, and staff assisting in the conduct of this clinical trial that the drugs are being used for investigational purposes, and I will ensure that the requirements relating to obtaining informed consent and IRB/IEC (in the US)/EC (in the EU) review and approval are met in accordance with national and regional legislation and the Declaration of Helsinki, and consistent with the recommendations in ICH E6.

All patients will be informed that they may withdraw from the clinical trial at their discretion at any time. I will use only the information sheet and consent form approved by the sponsor and the IRB/IEC (in the US)/EC (in the EU) which has reviewed this clinical trial.

I will provide the sponsor with any material written by myself (e.g., clinical trial summary) which is given to the IRB/IEC (in the US)/EC (in the EU) in support of the application. I agree to maintain adequate and accurate records and to make those records available for inspection in accordance with national and regional legislation and the Declaration of Helsinki, and consistent with the recommendations in ICH E6. I agree to the audit and monitoring procedures that involve verification of clinical trial records against the original records by direct access. In

case the source documentation and clinical trial data are kept electronically, I agree to ensure that these comply with the requirements on computerized systems and their validation in line with national and regional legislation and recommendations in ICH E6.

I will retain the trial-related essential documents until the sponsor informs me that these documents are no longer needed but no sooner than the requirements in national and regional legislation.

I certify that any laboratory, excluding the central laboratory (laboratories) appointed for the clinical trial, in which laboratory parameters will be determined, is subject to regular external quality control.

I agree to report to the sponsor adverse events that occur in the course of the clinical trial in accordance with national and regional legislation and the Declaration of Helsinki, and consistent with the recommendations in ICH E6. I have read and understand the information in the Investigator's Brochure, including the potential risks and side effects of the study intervention.

I agree to the collection, processing, transfer, use, and storing of my personal data and details relating to my professional activities for the purposes of the clinical trial by the sponsor and/or by a delegated party (e.g., a contract research organization).

I understand that the (e)CRFs and other data pertinent to this clinical trial are the property of the sponsor and are confidential. I will supply the sponsor with the clinical trial data in such a way that the patient's personal information and identity are protected.

I agree to comply with all other requirements regarding obligations of clinical investigators and with all other pertinent requirements in accordance with national and regional legislation and the Declaration of Helsinki. I also agree to follow the recommendations in ICH E6.

Investigator's signature: _____

Date: _____

Printed name: _____

Street address: _____

Telephone number: _____

Other contact information

Full contact details for each investigational site, the sponsor, and key coordinating and operational personnel involved in this clinical trial will be maintained in the Trial Master File and in the Investigator Site File.

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Change number	Description of change	Rationale for change	Section in Protocol Amendment 1
1	Addition of a urine pregnancy test to the End of treatment visit and in the Follow-up	Revised according to the Spanish Agency of Medicines and Health Products (AEMPS)'s (30Aug2022) and French Agency of Medicines and Health Products (ANSM)'s (06Dec2022) request for information	1.3 Schedule of activities
2	Timing of body weight assessment used for calculation of dose clarified to be made within 3 days prior to day 1	To allow use of the most current values for dose calculation	1.3 Schedule of activities
3	Addition of ECG assessment to day 1 of each cycle and End of treatment visit	Revised according to ANSM's request for information (06Dec2022):	1.3 Schedule of activities
4	Allowed visit window for safety laboratory samples adjusted	Revised to provide better guidance	1.3 Schedule of activities
5	Collection of samples for ADA determination in the treatment phase limited to cycle 2, 3 and 4	Sample frequency for determination of ADA at multiple intervals throughout the trial considered appropriate until 4 cycles and during follow up as per FDA guidance on Immunogenicity Testing of Therapeutic Protein Products.	1.3 Schedule of activities
6	Initial tumor scans can be taken with a visit window of 21 days before ICF signature	Revised to provide better guidance	1.3 Schedule of activities; 8.1.1 Initial tumor scans
7	PK sampling schedule adjusted	Adjusted on the basis of developed PK model for the optimization of sampling times of nanrilkefusp alfa	1.3 Schedule of activities
8	Benefit/risk assessment updated	To reflect new available data	2.3 Benefit/Risk assessment
9	PK and immunogenicity of cetuximab are to be determined as an exploratory endpoint	To allow collecting data as supportive only	1.1 Synopsis; 3 OBJECTIVES AND ENDPOINTS

Change number	Description of change	Rationale for change	Section in Protocol Amendment 1
10	Inclusion criterion no. 5 was modified, and criterion no. 6 was added with specification of tests to be used for confirmation of RAS wild type	Revised to provide better guidance for the screening process	5.1 Inclusion criteria
11	Inclusion no. 6 on EGFR mutation status availability was removed, information on status determination added into another section	To specify that EGFR status will be determined from biomarker samples	5.1 Inclusion criteria; 8-6 Biomarkers
12	Exclusion criterion no. 4 added to specify allowed lines of previous therapy to four	Revised to avoid bias in patient population	5.2 Exclusion criteria
13	Addition of management recommendations for cytokine release syndrome, shortening of the QT interval, increased ALT and/or AST, and injection site reaction	Revised according to ANSM's (06Dec2022) and Italian Agency of Medicines and Health Products (AIFA)'s (19Dec2022) request for information	6.5.1 Dose modification and toxicity management for nanrilkefusp alfa; 6.5.3 Clinical management of cytokine release syndrome
14	Guidance added on additional diagnostic measurements for patients with pre-existing pulmonary diseases and/or presence or suspicion of ILD and for patients with ophthalmological pre-conditions	Revised according to response to the Belgian Agency of Medicines and Health Products (AFMP)'s approval letter (23Sep2022)	6.5.4 Additional diagnostic measurements
15	Clarification added that safety assessments are to be done by local laboratories	To provide better guidance	8.2.5 Clinical safety laboratory assessments
16	Hy's law added and referred to in appendix 3	Revised according to Belgian Agency of Medicines and Health Products (AFMP)'s request for information (06Dec2022):	4.1.2 DLT definition; 10.3 Appendix 3: Hy's law

Change number	Description of change	Rationale for change	Section in Protocol Amendment 1
17	Cockcroft-Gault formula added and referred to in appendix 4	To provide better guidance	5.1 Inclusion criteria; 10.4 Appendix 4: Cockcroft-Gault formula
18	Sample size of patients specified to include patients from the safety cohorts and the main cohort	To improve clarity	1.2 Schema; 4.1.1 Study design; 9.5 Sample size determination
19	Change of "SOT101" to "nanrilkefusp alfa in Protocol body	Replacement of the product code "SOT101" to the International Nonproprietary Name "nanrilkefusp alfa" in the Protocol body for better clarity; product code stays "SOT101"	Throughout the document
20	Minor formatting/wording updates	To improve clarity	Throughout the document

DOCUMENT HISTORY	
Version	**Date**
Original Protocol	09May2022
Protocol Amendment ES-1	31Aug2022
Protocol Amendment FR-1	07Dec2022
Protocol Amendment IT-1	02Jan2023
Protocol Amendment 1	09Mar2023

TABLE OF CONTENTS

1 PROTOCOL SUMMARY

1.1 Synopsis

<table>
<tr><td>Study title</td><td>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)</td></tr>
<tr><td>Rationale</td><td>Cetuximab is a monoclonal IgG1 antibody which binds to the extracellular domain of EGFR and inhibits EGFR signaling, an important player in the initiation and progression of colorectal cancer. Cetuximab also triggers antibody-dependent cellular cytotoxicity (ADCC), an immune mechanism by which cells coated with IgG1 are destroyed by cells expressing CD16A (FcRIIIA), such as natural killer (NK) cells.
Nanrilkefusp alfa is a fusion protein which consists of the N-terminal domain of human interleukin (IL) 15 receptor α covalently coupled to human IL-15. In vitro, nanrilkefusp alfa augmented the antitumor activity of cetuximab by increasing NK cell-mediated ADCC. In clinical study SC103 (AURELIO-03; NCT04234113), nanrilkefusp alfa stimulated immune cell infiltration into tumors in clinically responsive patients which was accompanied by NK- and CD8+ T-cell activation and cytotoxicity.
It is hypothesized that nanrilkefusp alfa administered in combination with cetuximab can potentiate the tumor-directed ADCC and thus improve clinical outcomes in patients with EGFR positive, K-RAS/N-RAS wild-type colorectal cancer.</td></tr>
<tr><td>Overall design</td><td>Study SC105 (AURELIO-05) is a phase 2, open-label, single-arm, multicenter study of nanrilkefusp alfa in combination with cetuximab with an initial safety run-in with 3+3 safety cohorts.</td></tr>
<tr><td>Objectives and endpoints</td><td>
<table>
<tr><th>Objective</th><th>Endpoint(s)</th></tr>
<tr><td colspan="2">Primary</td></tr>
<tr><td>• To estimate the antitumor efficacy of nanrilkefusp alfa in combination with cetuximab</td><td>• Objective response rate (ORR) according to Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST 1.1)</td></tr>
<tr><td colspan="2">Secondary</td></tr>
<tr><td>• To further evaluate the antitumor efficacy of nanrilkefusp alfa in combination with cetuximab</td><td>• ORR according to RECIST for immune-based therapeutics (iRECIST) (iORR)</td></tr>
</table>
</td></tr>
</table>

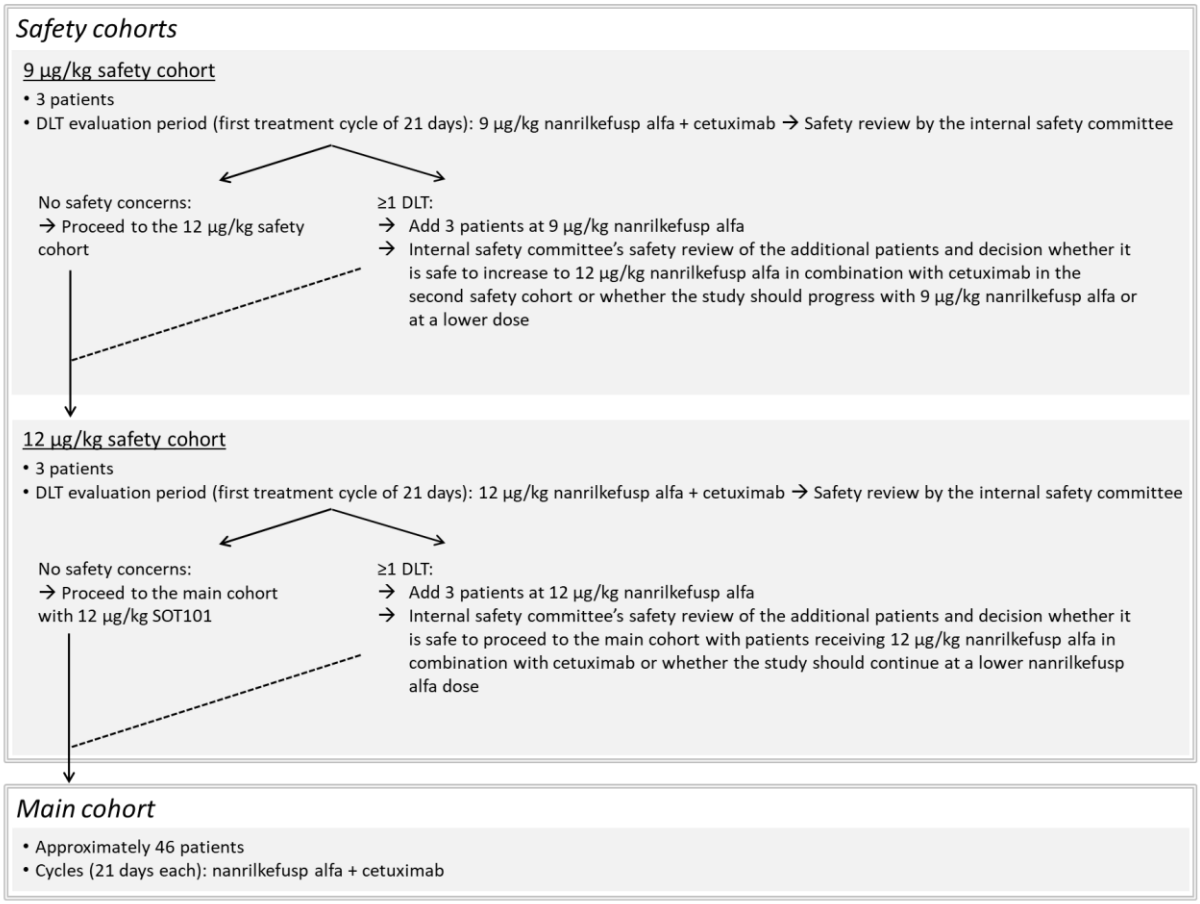
		• Best overall response according to RECIST 1.1 (BOR) and iRECIST (iBOR) • Duration of response according to RECIST 1.1 (DoR) and iRECIST (iDoR) • Clinical benefit rate according to RECIST 1.1 (CBR) and iRECIST (iCBR) • Progression-free survival (PFS) according to RECIST 1.1 and iRECIST (iPFS) • Time to response according to RECIST 1.1 (TtR) and iRECIST (iTtR) • Time to progression according to RECIST 1.1 (TtP) and iRECIST (iTtP)
	• To assess the safety and tolerability of nanrilkefusp alfa in combination with cetuximab	• Type, frequency, and severity of treatment-emergent adverse events according to Common Terminology Criteria for Adverse Events, version 5.0; safety laboratory findings; vital signs; electrocardiography findings
	• To determine the RP2D of nanrilkefusp alfa in combination with cetuximab	• Dose-limiting toxicities
	• To characterize the pharmacokinetics (PK) of nanrilkefusp alfa in a subset of patients	• Serum concentrations and calculated PK parameters of nanrilkefusp alfa
	• To determine the immunogenicity of nanrilkefusp alfa in combination with cetuximab	• Incidence, titer, and time course of anti-drug antibodies (ADAs) against nanrilkefusp alfa
	Exploratory	
	• To further evaluate the antitumor efficacy of	• PFS on next-line anti-cancer treatment (PFS2) • Overall survival (OS)

	nanrilkefusp alfa in combination with cetuximab	
	• To determine the status of immune-, molecular-, and disease-related biomarkers of potential importance	• Assessment of 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 DNA at screening and following nanrilkefusp alfa and cetuximab treatment
	• To determine the impact of the EGFR mutational status on efficacy	• Assessment of the EGFR mutational status at baseline and at disease progression
	• To characterize the PK of cetuximab in a subset of patients	• Serum concentrations and calculated PK parameters of cetuximab
	• To determine the immunogenicity of cetuximab in combination with nanrilkefusp alfa	• Incidence, titer, and time course of ADAs against cetuximab
Study interventions	Nanrilkefusp alfa will be administered subcutaneously 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. The dose of nanrilkefusp alfa for the main cohort of the study will be determined in the initial 3+3 safety cohorts. Cetuximab will be administered on day 1 (from cycle 2 onwards, ±1 day), day 8 (±1 day), and day 15 (±1 day) of each 21-day cycle. The initial dose of cetuximab will be 400 mg/m^2 body surface area administered as intravenous infusion over 120 minutes. All subsequent weekly doses will be 250 mg/m^2 each administered as intravenous infusion over 60 minutes. Prior to the first infusion of cetuximab, patients may receive premedication with an antihistamine and a corticosteroid at least 1 hour prior to administration of cetuximab. This premedication is recommended prior to all subsequent infusions. On day 1 and day 8, cetuximab infusion will start within 30 minutes after nanrilkefusp alfa administration.	
Study population	Patients with RAS wild-type colorectal cancer as confirmed by the investigational site within 3 months prior to the first administration of study treatment who are relapsed/refractory or intolerant to prior treatment with irinotecan- and oxaliplatin-containing chemotherapy	

Study duration	The study will end one year after the last patient's last dose of study treatment (nanrilkefusp alfa and/or cetuximab [whichever occurs later]) or 3 years after the last patient has received the first dose of nanrilkefusp alfa (whichever occurs earlier).
Estimated sample size	Approximately 52 patients
Statistical considerations	**Interim analysis, stopping/discontinuation criteria** 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 independent data monitoring committee (IDMC) review. 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% confidence interval (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: 1. lower than the minimal ORR, and 2. 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. **Statistical analyses** Summary statistics will include: • Counts and percentages (categorical data) • Number of observations, mean, standard deviation, median, minimum, and maximum (continuous data) The ORR, iORR, BOR, iBOR, CBR, and iCBR will use the exact method based on the binomial distribution to derive 95% CIs. Kaplan-Meier estimations and estimations of median (if reached) with log-log 95% CI, Q1 (25^{th} percentile), and Q3 (75^{th} percentile) will be used for DoR, iDoR, PFS, iPFS, TtR, iTtR, TtP, iTtP, PFS2, and OS. 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. The last value of CT scan or MRI on or up to 21 days before the date of the first study treatment will be used as the baseline value for each assessment. 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.
Internal safety committee	Applicable only to the safety cohorts: An internal safety committee (ISC) will be established for the safety cohorts of this study to evaluate patients' safety. The ISC will be tasked with making decisions based on their review to continue, modify, or stop recruitment or the trial based on their assessment of the safety data. The membership, key responsibilities, and the corresponding procedures will be defined in the ISC Charter.
Independent data monitoring committee	Applicable only to the main cohort: An independent data monitoring committee (IDMC) will be established for the main cohort to safeguard the interest and safety of the patients participating in the study and provide independent review and assessment of the efficacy and safety data in a systematic manner. The IDMC will be tasked with making a recommendation to the sponsor based on their review to continue, modify, or stop recruitment or the trial based on their assessment of efficacy and safety information. The membership, key responsibilities, and the corresponding procedures will be defined in the IDMC Charter.

1.2 Schema



The overall sample determined in this trial is 52 patients in efficacy population which includes patients from the safety cohorts and the main cohort.

1.3 Schedule of activities

Cycle	Screening Up to 21 days before day 1 of cycle 1	Cycle 1					From cycle 2 onwards					End of treatment* Within 7 (+7) days after the last dose of nanrilkefusp alfa and/or cetuximab (whichever occurs later)	Follow-up
Visit		**Day 1**	**Day 2** (±1 day)	**Day 8** (±1 day)	**Day 9** (±1 day)	**Day 15** (±1 day)	**Day 1** (±1 day)	**Day 2** (±1 day)	**Day 8** (±1 day)	**Day 9** (±1 day)	**Day 15** (±1 day)		
Informed consent[1]	X												
Demography[2]	X												
Cancer[3] **and medical history**	X												
K-RAS/N-RAS	X	Optional at disease progression											
Body height	X												
Pregnancy test	X (blood)[4]	X (urine)[5]					X (urine)[5]					X (urine)	X (urine) **
Physical examination	X[4]						X[7]					X	X[8]
Body weight and body surface area	X	X[9]					X[9]					X	
Vital signs	X	X[10]	X[10]	X[10]	X[10]	X[11]	X[10]	X[10]	X[10]	X[10]	X[11]	X	X[8]
Hematology[12]	X	X[6]	X[5]	X[6]	X[5]	X[5]	X[6]		X[6]		X[5]	X	
Biochemistry[12]	X	X[6]	X[5]	X[6]	X[5]	X[5]	X[6]		X[6]		X[5]	X	
Coagulation[12]	X	X[6,13]		X[6]		X[5]	X[6]				X[5]	X	
Urinalysis	X[4]						X[11]					X	
Creatinine clearance	X	X[11]					X[11]						
Electrocardiography	X	X[11]					X[11]					X	
Echocardiography/multiple gated acquisition scanning	X												

Cycle	Screening Up to 21 days before day 1 of cycle 1	Cycle 1					From cycle 2 onwards					End of treatment* Within 7 (+7) days after the last dose of nanrilkefusp alfa and/or cetuximab (whichever occurs later)	Follow-up
Visit		**Day 1**	**Day 2** (±1 day)	**Day 8** (±1 day)	**Day 9** (±1 day)	**Day 15** (±1 day)	**Day 1** (±1 day)	**Day 2** (±1 day)	**Day 8** (±1 day)	**Day 9** (±1 day)	**Day 15** (±1 day)		
Eastern Cooperative Oncology Group performance score	X[4]	X[11]					X[11]					X	X[8]
Tumor assessment (CT/MRI)	X[14]	Every 6 weeks (±2 weeks) starting from day 1 of cycle 1 until confirmed disease progression per iRECIST, start of next-line anti-cancer treatment, pregnancy of the patient, withdrawal of consent by the patient, or end of the study											
Nanrilkefusp alfa administration[15]		X	X	X	X		X	X	X	X			
Cetuximab administration[16]		X		X		X	X		X		X		
Adverse events	X	X											X[8,17]
Concomitant medication/ non-drug therapies	X	X											X[8,17]
HIV, hepatitis B and C	X												
Serum for nanrilkefusp alfa pharmacokinetics	See Table 1.1												
Serum for nanrilkefusp alfa anti-drug antibodies		X[11]					X[11,18]						X[8]
Serum for cetuximab pharmacokinetics	See Table 1.1												
Serum for cetuximab anti-drug antibodies		X[11]					X[11,18]						X[8]
Serum for cytokines		X[19]					X[19,20]						
Whole blood for exploratory biomarkers		X[11,21]					X[11]						
Survival status													X[22]
Next-line anti-cancer treatment													X[22]
Date of progression on next-line anti-cancer treatment													X

* Criteria for discontinuation of study interventions are listed in section 7.1.
** Every 30 (±2) days until 60 (±2) days after the last dose of cetuximab or 30 (±2) days after the last dose of nanrilkefusp alfa, whichever is later
1. No study-specific procedures are to be performed before Informed Consent Form signature
2. Age at screening and gender
3. Primary tumor location, histology/cytology, initial diagnosis date, lines of previous treatment, start and stop dates of the treatments before this study, any prior mutations/genetic analysis (e.g., EGFR, K-RAS/N-RAS mutations), and the date of the latest disease progression if not coinciding with the stop date
4. Within 7 days before day 1 of cycle 1
5. On the day of dosing before nanrilkefusp alfa administration and/or cetuximab administration
6. Sample can be taken within 24 hours before nanrilkefusp alfa and/or cetuximab administration
7. Before nanrilkefusp alfa administration and afterwards as clinically required
8. Follow-up visit 30 (±2) days after the last dose of nanrilkefusp alfa and/or cetuximab (whichever occurs later)
9. Last body weight assessment within 3 days prior to day 1 should be used for dose calculation.
10. Before and after nanrilkefusp alfa administration as described in section 8.2.3
11. Before nanrilkefusp alfa and/or cetuximab administration
12. Additional samples may be taken as clinically indicated
13. Before nanrilkefusp alfa administration and 2 hours (±15 min) after nanrilkefusp alfa administration
14. Tumor scans performed as part of routine clinical management are acceptable for screening if they are of acceptable diagnostic quality and performed within 21 days prior to ICF signature
15. Time to be recorded
16. Time to be recorded; on day 1 and day 8, cetuximab infusion will start within 30 minutes after nanrilkefusp alfa administration
17. Contact 90 (+2) days after the last dose of nanrilkefusp alfa and/or cetuximab (whichever occurs later)
18. To be collected up to cycle 4
19. Before nanrilkefusp alfa administration and 6 hours (±15 min) after nanrilkefusp alfa administration
20. Only in cycle 2
21. Samples for Fc gamma receptor polymorphism only in cycle 1
22. Contact 90 (+2) days after the last dose of nanrilkefusp alfa and/or cetuximab (whichever occurs later) and then at 3-month (±2 weeks) intervals until the end of the study

Table 1.1: Pharmacokinetic sampling

Serum samples will be collected from all patients in the initial safety cohorts and from the first 12 patients in the main cohort. All attempts should be made to collect the samples on time.

Cycle, day	Time point	Nanrilkefusp alfa	Cetuximab
Cycle 1 day 1	Pre-dose to nanrilkefusp alfa and cetuximab	X	X
	30 min (±5 min)	X	
	1 h (±5 min)	X	
	2 h (±15 min)	X	X
	4 h (±30 min)	X	X
	12 h (±2 h), if logistically possible	X	
Cycle 1 day 2	Pre-dose to cycle 1 day 2 nanrilkefusp alfa[1] (-2 h [-15 min] to 0 h)	X	
Cycle 1 day 8	Pre-dose to cycle 1 day 8 nanrilkefusp alfa and cetuximab[1] (-2 h [-15 min] to 0 h)	X	X
Cycle 1 day 9	Pre-dose to cycle 1 day 9 nanrilkefusp alfa[1] (-2 h [-15 min] to 0 h)	X	
	2 h (±15 min)	X	
	4 h (±30 min)	X	
Cycle 1 day 15	Pre-dose to cycle 1 day 15 cetuximab[1] (-2 h [-15 min] to 0 h)		X
Cycle 3 day 1	Pre-dose to nanrilkefusp alfa and cetuximab[1] (-2 h [-15 min] to 0 h)	X	X
	2 h (±15 min)	X	X

[1] Sample to be taken as early as possible when patients arrive at site

2 INTRODUCTION

2.1 Study rationale

Cetuximab is a monoclonal IgG1 antibody which binds to the extracellular domain of EGFR and inhibits EGFR signaling, an important player in the initiation and progression of colorectal cancer.[1,2] Cetuximab also triggers antibody-dependent cellular cytotoxicity (ADCC), an immune mechanism by which cells coated with IgG1 are destroyed by cells expressing CD16A (FcRIIIA), such as natural killer (NK) cells.[3]

Nanrilkefusp alfa is a fusion protein which consists of the N-terminal domain of human interleukin (IL) 15 receptor α covalently coupled to human IL-15.[4] *In vitro*, nanrilkefusp alfa augmented the antitumor activity of cetuximab by increasing NK cell-mediated ADCC.[5] In clinical study SC103 (AURELIO-03; NCT04234113), nanrilkefusp alfa stimulated immune cell infiltration into tumors in clinically responsive patients which was accompanied by NK- and CD8+ T-cell activation and cytotoxicity.[6]

It is hypothesized that nanrilkefusp alfa administered in combination with cetuximab can potentiate the tumor-directed ADCC and thus improve clinical outcomes in patients with EGFR positive, K-RAS/N-RAS wild-type colorectal cancer.

2.2 Background

Colorectal cancer is the third most commonly diagnosed cancer and a leading cause of death worldwide. In 2020, there were over 1.9 million new cases with an estimated 935,173 deaths.[7]

EGFR signaling is one of a number of different molecular pathways involved in the development and progression of colorectal cancer.[8] Ligand binding stimulates the tyrosine kinase domain of EGFR and leads to receptor dimerization and activation of several downstream effectors, such as K-RAS/N-RAS, that activate cell proliferation and tumor metastasis.[1,2,9] K-RAS/N-RAS are effector molecules responsible for signal transduction from ligand-bound EGFR to the nucleus. Activating mutations in K-RAS/N-RAS are able to bypass EGFR signaling and lead to tumor progression independently of EGFR.[9,10]

The choice of the optimal therapeutic strategy for each patient with metastatic colorectal cancer depends on a number of parameters, including clinical status, blood counts, liver and renal functions, measurement of tumor markers, and abdominal and thoracic CT/MRI. Patients with resectable disease are referred for surgery or perioperative chemotherapy to achieve complete resection. Patients with unresectable disease and fit for systemic treatment are treated with intravenous 5-fluorouracil in various combinations and schedules with irinotecan or oxaliplatin, oral capecitabine in combination with oxaliplatin, bevacizumab, and EGFR antibodies panitumumab and cetuximab.[11,12]

Cetuximab, a recombinant chimeric monoclonal IgG1 antibody, binds to the extracellular domain of EGFR, inhibits EGFR ligand binding and dimerization, and induces EGFR internalization.[13] Cetuximab also triggers ADCC, an immune mechanism by which cells coated with IgG1 are destroyed by cells expressing the activating Fc gamma receptor CD16A (FcRIIIA), such as NK cells.[3]

Unfortunately, most patients develop resistance to cetuximab caused by increased activation of other receptor tyrosine kinases and downstream signaling pathways. New treatment options are therefore needed to prevent or overcome this resistance.

In colorectal cancer, circulating NK cells exhibit a dysregulated phenotype compared to NK cells from normal human donors and demonstrate defective functionality and altered interferon gamma production.[14]

It is hypothesized that combination treatment with a cytokine therapy that directly improves NK cell activity and/or functionality via increased expression of CD16 or indirectly increases cell fitness and activity will enhance the ADCC of cetuximab and thus may offer a new opportunity to better treat colorectal cancer.[15] Using preclinical models, it was observed that IL-2 and IL-15 combined with cetuximab stimulated NK cells and improved their cytotoxicity.[14]

Nanrilkefusp alfa is a fusion protein of the N-terminal sushi domain of human IL-15 receptor α covalently coupled via a linker of 20 amino acids to human IL-15.[4] *In vitro*, nanrilkefusp alfa induced proliferation and expansion of both major subsets of human NK cells, $CD56^{bright}CD16^{-}$ and $CD56^{dim}CD16^{+}$. Furthermore, nanrilkefusp alfa induced expression of the cytotoxic receptors NKp30 and NKG2D, whereas no upregulation of the inhibitory receptors CD158a, CD158b, and NKG2A was detected. Both NK cell subsets activated by nanrilkefusp alfa exhibited cytotoxicity towards cancer cells, and nanrilkefusp alfa augmented the antitumor activity of cetuximab by increasing NK cell-mediated ADCC.[5] In the murine CT26 colorectal carcinoma model, nanrilkefusp alfa monotherapy treatment induced proliferation of NK and CD8+ memory T cells and significantly decreased tumor growth to about 40% on day 30.[16] In clinical study SC103 (AURELIO-03; NCT04234113; a multicenter, open-label, phase 1/1b study to evaluate the safety and preliminary efficacy of nanrilkefusp alfa as monotherapy and in combination with pembrolizumab in patients with selected advanced/metastatic solid tumors), nanrilkefusp alfa stimulated immune cell infiltration into tumors in clinically responsive patients which was accompanied by NK and CD8+ T-cell activation and cytotoxicity.[6] Two patients with colorectal cancer were treated in this study with nanrilkefusp alfa in combination with pembrolizumab; one patient at 6.0 µg/kg nanrilkefusp alfa and the other at 9.0 µg/kg nanrilkefusp alfa. The patient treated with 9.0 µg/kg nanrilkefusp alfa, a dose one dose level below the recommended phase 2 dose (RP2D), achieved confirmed stable disease according to iRECIST.

Based on the above results from pre-clinical studies and preliminary results from study AURELIO-03, it is hypothesized that nanrilkefusp alfa administered in combination with cetuximab could improve NK cell activity and/or functionality via increased expression of CD16 or indirectly increase cell fitness and activity to enhance the ADCC of cetuximab and thus may offer a new opportunity to better treat K-RAS/N-RAS wild-type advanced and/or metastatic colorectal cancer.

2.3 Benefit/risk assessment

The risk assessment of nanrilkefusp alfa is based on nonclinical studies in addition to clinical experience from completed and ongoing trials with nanrilkefusp alfa as monotherapy and in combination with pembrolizumab. Clinical safety data from study SC103 (AURELIO-03) in patients with advanced/metastatic solid tumors for nanrilkefusp alfa in combination with pembrolizumab showed a similar profile as for nanrilkefusp alfa monotherapy; no relevant overlapping toxicities were reported. The majority of treatment-emergent adverse events (TEAEs) were of grade 1 or 2. As of 11Apr2022 (cut-off date for AURELIO-03), the most common TEAEs for nanrilkefusp alfa monotherapy / nanrilkefusp alfa in combination with pembrolizumab were pyrexia (70.0/81.0%), decreased lymphocyte count (66.7/47.6%), anemia

(60.0/52.4%), injection site reaction (56.7/57.1%), and chills (50.0/61.9%). The most common TEAEs of grade >2 were decreased lymphocyte, anemia, and pyrexia. These TEAEs could be well managed and were self-limiting upon discontinuation of nanrilkefusp alfa.

The present combination nanrilkefusp alfa/cetuximab study will start with a safety cohort at 9 µg/kg nanrilkefusp alfa, which is one dose level below the nanrilkefusp alfa RP2D of 12 µg/kg. It is hypothesized that nanrilkefusp alfa in combination with cetuximab enhances tumor-directed ADCC and thus improves the clinical outcome in patients with RAS wild-type colorectal cancer.

Preliminary efficacy results in study SC103 (AURELIO-03) in advanced/metastatic solid tumors were encouraging, showing clinical benefit for most patients in the combination part of the study, including patients pretreated with immune checkpoint inhibitors. Maximum activation of natural killer cells was observed already at low dose levels of nanrilkefusp alfa, and maximum activation of CD8+ T-cells was reached at 9 to 12 µg/kg nanrilkefusp alfa.

More recent information about the known and expected benefits and risks and adverse events (AEs) that could be associated with the administration of nanrilkefusp alfa and cetuximab may be found in the Investigator's Brochure (IB) and Erbitux's current package insert/US prescribing information (for the US)[17] and current summary of product characteristics (SmPC; for the EU).[18]

In conclusion, the current nonclinical and clinical data on nanrilkefusp alfa in patients with advanced/metastatic solid tumors suggest a favorable benefit/risk ratio and justify further clinical development of nanrilkefusp alfa.

3 OBJECTIVES AND ENDPOINTS

Objective	Endpoint(s)
Primary	
• To estimate the antitumor efficacy of nanrilkefusp alfa in combination with cetuximab	• Objective response rate (ORR) according to Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST 1.1)[19]
Secondary	
• To further evaluate the antitumor efficacy of nanrilkefusp alfa in combination with cetuximab	• ORR according to RECIST for immune-based therapeutics (iRECIST)[20] (iORR) • Best overall response according to RECIST 1.1 (BOR) and iRECIST (iBOR) • Duration of response according to RECIST 1.1 (DoR) and iRECIST (iDoR) • Clinical benefit rate according to RECIST 1.1 (CBR) and iRECIST (iCBR) • Progression-free survival (PFS) according to RECIST 1.1 and iRECIST (iPFS) • Time to response according to RECIST 1.1 (TtR) and iRECIST (iTtR) • Time to progression according to RECIST 1.1 (TtP) and iRECIST (iTtP)
• To assess the safety and tolerability of nanrilkefusp alfa in combination with cetuximab	• Type, frequency, and severity of TEAEs according to Common Terminology Criteria for Adverse Events (CTCAE), version 5.0; safety laboratory findings; vital signs; electrocardiography findings
• To determine the RP2D of nanrilkefusp alfa in combination with cetuximab	• Dose-limiting toxicities (DLTs)
• To characterize the pharmacokinetics (PK) of nanrilkefusp alfa in a subset of patients	• Serum concentrations and calculated PK parameters of nanrilkefusp alfa

Objective	Endpoint(s)
• To determine the immunogenicity of nanrilkefusp alfa in combination with cetuximab	• Incidence, titer, and time course of anti-drug antibodies (ADAs) against nanrilkefusp alfa
Exploratory	
• To further evaluate the antitumor efficacy of nanrilkefusp alfa in combination with cetuximab	• PFS on next-line anti-cancer treatment (PFS2) • Overall survival (OS)
• To determine the status of immune-, molecular-, and disease-related biomarkers of potential importance	• Assessment of 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 DNA at screening and following nanrilkefusp alfa and cetuximab treatment
• To determine the impact of the EGFR mutational status on efficacy	• Assessment of the EGFR mutational status at baseline and at disease progression
• To characterize the PK of cetuximab in a subset of patients	• Serum concentrations and calculated PK parameters of cetuximab
• To determine the immunogenicity of cetuximab in combination with nanrilkefusp alfa	• Incidence, titer, and time course of ADAs against cetuximab

4 STUDY DESIGN

4.1 Overall 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. For an overview of the study design please refer to section 1.2.

4.1.1 Study design

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 RP2D as determined in study SC103 (AURELIO-03) which evaluated nanrilkefusp alfa at doses up to 12 µg/kg in combination with pembrolizumab. Please see section 6.1 for more details on administration of study interventions.

After the last patient in the 9 µg/kg safety cohort completes the first treatment cycle of 21 days, i.e., the 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 (see section 4.1.3) 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. 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.

4.1.2 DLT definition

For the safety cohorts, DLTs will be AEs listed below, specified and graded according to CTCAE, version 5.0, without consideration of causality to nanrilkefusp alfa. AEs listed below will be considered DLTs unless clearly not related to nanrilkefusp alfa (i.e., events clearly due to cancer, other comorbid illness, or unequivocally related to concomitant medications).

Every DLT in the study will be discussed with the study investigators and every effort will be made to ensure all clinical assessments are carried out and documented appropriately and, wherever possible, histological assessments are also performed to identify and understand the safety profile of nanrilkefusp alfa in combination with cetuximab.

AEs that are considered DLTs

- All grade 5 events not clearly related to disease progression or any other causes will be considered DLTs.
- Any grade 3 or higher non-hematologic toxicity regardless of duration will be considered a DLT, with the following exceptions that are not considered DLTs:
  - Grade 3 nausea, vomiting, or diarrhea that can be controlled within 72 hours
  - Grade 3 fatigue that lasts less than 5 days
  - Grade 3 or higher correctable electrolyte abnormalities that last less than 72 hours and are not associated with clinical complications
  - Grade 3 or higher serum amylase or lipase not associated with clinical manifestations of pancreatitis
  - Grade 3 aspartate aminotransferase (AST) or alanine aminotransferase (ALT) increase or grade 3 blood bilirubin increase that lasts 5 days or less
- Hy's law cases will be considered DLTs (see section 10.3).
- Hematologic DLTs will include the following:
  - Grade 4 decreased neutrophil count or decreased platelet count lasting more than 7 days
  - Febrile neutropenia
  - Grade 3 or higher decreased platelet count with bleeding

AEs that are not considered DLTs

- Inflammatory reaction attributed to a local antitumor response (grade 3 tumor pain caused by acute inflammatory reaction at tumor-bearing sites, e.g., like sites of metastatic disease or lymph nodes) that resolves to grade 1 within 3 weeks
- Concurrent vitiligo or alopecia of any CTCAE grade

Other clinically significant toxicities, including a single event or multiple occurrences of the same event, may be considered DLTs in the safety cohorts.

4.1.3 DLT evaluability

DLT evaluability is defined 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)

4.1.4 Study periods

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

4.1.4.1 Screening

Patients will be screened within a period of not more than 21 days, which will start when the Informed Consent Form (ICF) has been signed and end before day 1 of cycle 1.

4.1.4.2 Treatment

During the treatment period, study interventions will be administered as described in section 6 until any of the criteria for discontinuation of study interventions is met (see section 7.1).

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).

4.1.4.3 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 defined in section 4.4.

4.2 Scientific rationale for study design

The AURELIO-05 study is designed as an open-label, single-arm, phase 2 proof-of-concept clinical trial with nanrilkefusp alfa in combination with cetuximab in patients with metastatic colorectal cancer. The study design represents a standard approach in early phase 2 clinical trials where the main aim is to investigate preliminary efficacy signals in an appropriate time frame to enable further clinical evaluation in a subsequent confirmatory clinical trial setting.

The primary endpoint of this study is ORR according to RECIST 1.1. This endpoint has the advantage of being generally assessed earlier and with a smaller sample size compared to time-to-event endpoints. The evaluation of ORR is generally also based on objective and quantitative assessments, i.e., radiological tumor assessments based on the widely accepted RECIST 1.1 response criteria.

In the AURELIO-05 study, the ORR of cetuximab monotherapy in patients with metastatic colorectal cancer with disease progression or intolerance to irinotecan-based and oxaliplatin-based therapy was used as benchmark for the sample size calculation. The target ORR of approximately 37% for the nanrilkefusp alfa + cetuximab combination therapy versus 20% for

cetuximab monotherapy[21] appears to be an additional clinically relevant benefit for patients with metastatic colorectal cancer, as discussed and confirmed by clinical experts in the colorectal cancer field.

4.3 Justification for dose

4.3.1 Nanrilkefusp alfa (SOT101)

In study SC103 (AURELIO-03), 12 µg/kg of nanrilkefusp alfa was determined to be the RP2D for both nanrilkefusp alfa monotherapy and nanrilkefusp alfa combined with pembrolizumab. To ensure that it is safe to administer nanrilkefusp alfa at this RP2D together with cetuximab, an initial safety cohort of 3 patients will be treated with cetuximab in combination with 9 µg/kg nanrilkefusp alfa, a dose one dose level below the RP2D determined in study SC103 (AURELIO-03). These 3 patients will be closely observed, and safety data collected during the DLT assessment period, i.e., first 21-day treatment cycle, will be evaluated by the ISC. If the safety of nanrilkefusp alfa at 9 µg/kg in combination with cetuximab is acceptable, another safety cohort of 3 patients will be treated with cetuximab in combination with 12 µg/kg nanrilkefusp alfa, the RP2D determined in study SC103 (AURELIO-03). Safety in the 12 µg/kg cohort will be evaluated by the ISC after the last patient completes the DLT assessment period. 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. If there are safety concerns at the 9 µg/kg and/or 12 µg/kg nanrilkefusp alfa safety cohorts, the ISC will decide how to proceed as described in section 4.1.1.

4.3.2 Cetuximab

Cetuximab and its required comedications will be administered as described in section 6.1.

4.4 End of study definition

A patient is considered to have completed the study if s/he has completed all phases of the study including the last follow-up visit or contact in the study (whichever occurs later).

The study will end one year after the last patient's last dose of study treatment (nanrilkefusp alfa and/or cetuximab [whichever occurs later]) or 3 years after the last patient has received the first dose of nanrilkefusp alfa (whichever occurs earlier).

The sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If the study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions, regulatory agencies, and institutional review board (IRB) / independent ethics committee (IEC; in the US) or ethics committee (EC; in the EU) of the termination or suspension and the reason(s) for the termination or suspension.

The investigator reserves the right to discontinue the study for his/her investigational site, should his/her judgment so dictate. If the investigator terminates or suspends the study without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC (in the US) / EC (in the EU) and provide the sponsor and the IRB/IEC (in the US) / EC (in the EU) with a detailed written explanation of the termination or suspension.

5 STUDY POPULATION

5.1 Inclusion criteria

Patients will be eligible to be included in the study only if all of the following criteria apply:

Type of patients

1. ≥18 years of age on the day of signing informed consent
2. Ability to understand and sign written informed consent to participate in the study
3. Provides written informed consent for the study
4. Life expectancy >6 months

Disease characteristics

5. Histologically or cytologically confirmed advanced and/or metastatic colorectal cancer
6. RAS wild type as confirmed by:
    - locally performed US Food and Drug Administration (FDA)-approved test or an experienced local laboratory using validated test methods for the detection, based on tumor biopsy or
    - locally performed ctDNA assessment including at least mutations in exon 2 (G12D, G12V, G12C, G12S, G12A, G12R, G13D) and determined by a laboratory using validated test methods
    - samples must be taken within 3 months prior to first study administration
7. Patients who are relapsed/refractory or intolerant to prior treatment with irinotecan- and oxaliplatin-containing chemotherapy
8. Have at least one measurable lesion according to RECIST 1.1
9. Eastern Cooperative Oncology Group (ECOG) performance score 0-2
10. Must have recovered from all AEs due to previous therapies to grade ≤1 toxicity (excluding alopecia)

Organ function

Have adequate organ function as defined below. Specimens must be collected within 7 days prior to the start of study treatment.

11. Hematology:
    11.1. Absolute neutrophil count ≥1,500/μL
    11.2. Platelets ≥100,000/μL
    11.3. Hemoglobin ≥9.0 g/dL (criteria must be met without packed red blood cell transfusion within the prior 2 weeks; patients can be on stable dose of erythropoietin [≥3 months])
12. Renal function: Creatinine clearance rate ≥50 mL/min as calculated using Cockcroft-Gault equation (see section 10.4)

13. Hepatic function: ALT/AST ≤2.5× upper limit of normal (ULN) and total bilirubin ≤2×ULN in patients without liver metastasis (benign hereditary hyperbilirubinemias, e.g., Gilbert's syndrome, are permitted if total bilirubin <3 mg/dL). In patients with liver metastasis, ALT/AST ≤5×ULN is allowed but total bilirubin must be ≤2×ULN.
14. Prothrombin time and activated partial thromboplastin time ≤1.5×ULN

Hepatitis

15. A locally performed hepatitis B (HBV) test is required during screening. Patients who are HBV surface antigen positive are eligible if they have received HBV anti-viral therapy for at least 4 weeks and have undetectable HBV viral load before study entry (ICF signature). Patients should remain on anti-viral therapy throughout study treatment and follow local guidelines for HBV anti-viral therapy post completion of study treatments.
16. A locally performed hepatitis C (HCV) test is required during screening. Patients with history of HCV infection are eligible if HCV viral load is undetectable at screening. Patients must have completed anti-viral therapy at least 4 weeks before study entry (ICF signature).

Special requirements for contraception

17. A female patient is eligible to participate if she is not pregnant, not breastfeeding, and one of the following conditions applies:
    - 17.1. Not a woman of childbearing potential (WOCBP). A WOCBP is defined as fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single follicle stimulating hormone measurement is insufficient.
    - 17.2. A WOCBP who agrees to use a highly effective contraceptive method during the treatment period and for at least 60 days after the last dose of cetuximab or at least 30 days after last dose of nanrilkefusp alfa, whichever is later.
        - WOCBP can only be included after a negative serum pregnancy test at screening within 7 days before day 1 of cycle 1.
        - Highly effective contraception includes:
            - Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
                - Oral
                - Intravaginal
                - Transdermal
            - Progestogen-only hormonal contraception associated with inhibition of ovulation:
                - Oral

- Injectable
- Implantable

- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner provided the partner is the sole sexual partner of the WOCBP trial participant and that the vasectomized partner has received medical assessment of the surgical success.
- Sexual abstinence defined as refraining from heterosexual intercourse during the entire treatment period and for at least 60 days after the last dose of cetuximab or at least 30 days after last dose of nanrilkefusp alfa, whichever is later. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

18. Male patients must agree to use a condom during the treatment period and for at least 60 days after the last dose of cetuximab or at least 30 days after last dose of nanrilkefusp alfa, whichever is later.

5.2 Exclusion criteria

Patients will be excluded from the study if any of the following criteria apply:

Prior/concomitant therapy

1. Prior exposure to drugs that are agonists of IL-2 or IL-15
2. Therapy with cetuximab within 3 months prior to ICF signature or patients who had progressive disease as best response to prior cetuximab-containing regimen
3. Prior systemic anti-cancer therapies, including investigational agents before study entry (ICF signature):
   3.1. Less than 3 weeks or 5 half-lives (whichever shorter) for anti-cancer treatments
   3.2. Less than 4 weeks from major surgeries and not recovered adequately from the procedure and/or any complications from the surgery
4. Has received more than 4 prior lines of systemic anticancer treatment
5. Has received prior radiotherapy within 2 weeks of the start of study treatments. A 1-week radiation-free period is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-central nervous system disease. Patients must have recovered from all radiation-related toxicities and not require corticosteroids.
6. Has received a live or live-attenuated vaccine within 30 days prior to the first dose of study treatments

Prior/concurrent clinical study experience

7. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 3 weeks or 5 half-lives (whichever longer) before

study entry (ICF signature). Patients who have entered the follow-up phase of an investigational study may participate as long as it has been 3 weeks or 5 half-lives (whichever longer) after the last dose of the previous investigational agent.

Medical conditions

8. Patients with known BRAF mutations
9. Clinically significant cardiac abnormalities including prior history of any of the following:
   - 9.1. Cardiomyopathy, with left ventricular ejection fraction lower than the lower limit of the institutional normal range at screening
   - 9.2. Congestive heart failure of New York Heart Association grade ≥2
   - 9.3. History of clinically significant (i.e., active) atherosclerotic cardiovascular disease, specifically myocardial infarction, unstable angina, cerebrovascular accident within 6 months prior to the first dose of study treatments, and any history of coronary heart disease and clinically significant peripheral and/or carotid artery disease
   - 9.4. Prolongation of QTcF >450 msec; history or family history of congenital long QT syndrome
   - 9.5. Uncontrolled cardiac arrhythmia requiring medication
10. Uncontrolled hypertension defined as systolic blood pressure >160 mmHg, diastolic blood pressure >110 mmHg. Patients with uncontrolled hypertension should be medically managed on a stable regimen to control hypertension prior to study entry (ICF signature).
11. Has a clinical diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatments. Systemic steroid pretreatment prior to cetuximab infusion according to local guidelines is permitted.
12. History of or serology positive for HIV. A locally performed HIV test is required during screening.
13. Has a known additional malignancy that is progressing or has required active treatment within the past 5 years. Patients with basal cell carcinoma of the skin or carcinoma *in situ* (e.g., breast carcinoma, cervical cancer *in situ*) that have undergone potentially curative therapy are eligible.
14. Has known active central nervous system metastases and/or carcinomatous meningitis. Patients with previously treated brain metastases may participate provided they are radiologically stable, i.e., without evidence of progression for at least 4 weeks confirmed during screening.
15. Has an active autoimmune disease that has required systemic treatment in the past 2 years (i.e., with use of disease-modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.
16. Has an active infection requiring systemic therapy

17. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the patient's participation for the full duration of the study, or is not in the best interest of the patient to participate, in the opinion of the treating investigator
18. Has a known psychiatric or substance abuse disorder that would interfere with the patient's ability to cooperate with the requirements of the study
19. History of hypersensitivity to any component of cetuximab or to compounds of similar biological or chemical composition of nanrilkefusp alfa and/or the excipients contained in the study drug formulations

5.3 Lifestyle considerations

5.3.1 Meals and dietary restrictions

Patients should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting.

5.3.2 Contraception

Nanrilkefusp alfa may have adverse effects on a fetus *in utero*. Furthermore, it is not known if nanrilkefusp alfa has transient adverse effects on the composition of sperm.

Based on findings from animal studies and its mechanism of action, cetuximab can cause fetal harm when administered to a pregnant woman.

Patients should be informed that taking the study treatment may involve risks to the fetus if pregnancy were to occur during the study. If there is any question that a patient of childbearing potential will not reliably comply with the requirements for contraception, that patient should not be entered into the study.

Please also see section 5.1.

5.3.3 Use in nursing women

It is unknown whether nanrilkefusp alfa and cetuximab are excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, patients who are breastfeeding are not eligible for enrollment.

Please also see section 5.1.

5.4 Screen failures

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently entered into the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, reason for screen failure, and AE/serious AE (SAE).

Patients may be rescreened once.

5.5 Criteria for temporarily delaying enrollment/ administration of study intervention

See section 6.5.

6 STUDY INTERVENTIONS AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study patient according to the study Protocol.

6.1 Study interventions administered

The interventions to be administered in this study are listed in Table 6.1.

Prophylactic antibiotic therapy (e.g., oral lymecycline or doxycycline) to prevent EGFR inhibitor-related skin toxicities are permitted according to local guidelines.

Prior to the first infusion of cetuximab, patients may receive premedication with an antihistamine and a corticosteroid at least 1 hour prior to administration of cetuximab. This premedication is recommended prior to all subsequent infusions.

Nanrilkefusp alfa subcutaneous injection sites will be rotated to different areas of the body (upper and lower extremities, each of the 4 quadrants of the abdomen) to minimize the summated local effects of nanrilkefusp alfa administration.

The pharmacy manual contains specific instructions for the preparation of the nanrilkefusp alfa dose and cetuximab infusion and administration of nanrilkefusp alfa and cetuximab.

Table 6.1: 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	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
Cetuximab Investigational intervention	Solution for infusion	5 mg/mL	Initial dose: 400 mg/m^2 body surface area 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

6.2 Preparation, handling, storage, accountability

The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study interventions.

Only patients enrolled in the study may receive study interventions and only authorized site staff may supply or administer study interventions. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study interventions are provided in the pharmacy manual.

6.3 Measures to minimize bias: randomization and blinding

This is a single-arm clinical trial, randomization and blinding do not apply.

6.4 Study intervention compliance

Treatment for each patient will be recorded during the study.

6.5 Dose modification and toxicity management

6.5.1 Dose modification and toxicity management for nanrilkefusp alfa

Dose modification and toxicity management for nanrilkefusp alfa for safety reasons, will be discussed on a case-by-case basis between the site and the sponsor's medical monitor. Recommendations for clinical management of cytokine release syndrome are provided in Table 6.4.

To minimize the risk for injection site reaction, subcutaneous injection sites should be rotated to different areas of the body (upper and lower extremities, each of the 4 quadrants of the abdomen) to minimize the summated local effects of nanrilkefusp alfa administration.

To minimize the risks associated with shortening of the QT interval, vital signs and electrocardiography (ECG) must be closely monitored as per Protocol and institutional guidelines.

Liver function tests for nanrilkefusp alfa toxicity evaluation in this study will include AST, ALT, total bilirubin, and alkaline phosphatase.

Nanrilkefusp alfa-related hepatic toxicities should be managed as shown in Table 6.2.

Table 6.2: Management of nanrilkefusp alfa-related hepatic toxicities

Nanrilkefusp alfa-related hepatic toxicity	Severity	Nanrilkefusp alfa dose modification
AST increased or ALT increased, or blood bilirubin increased	Grade 2 with AST or ALT >3 to ≤5×ULN or total bilirubin >1.5 to ≤3×ULN	Withhold nanrilkefusp alfa Resume nanrilkefusp alfa if increased values return to grade ≤1
	Grade ≥3 with AST or ALT >5×ULN or total bilirubin >3×ULN	Withhold nanrilkefusp alfa Resume nanrilkefusp alfa at one dose level below or reduce by 3 µg/kg if increased values return to grade ≤1 Permanently discontinue nanrilkefusp alfa on second occurrence of grade ≥3 hepatic event

Please also refer to the IB, section 6.6 (Management guidelines for identified and potential risks).

6.5.2 Dose modification and toxicity management for cetuximab

Cetuximab should be reduced, delayed, or discontinued to manage adverse reactions as described in Table 6.3.

Table 6.3: Recommended dose modifications of cetuximab for adverse reactions

Adverse reaction	Severity (CTCAE, version 5.0)	Dose modification
Infusion reactions	Grade 1	Reduce the infusion rate by 50%. Infuse under close supervision.
	Grade 2	Reduce the infusion rate by 50%. Immediately administer treatment for symptoms.
	Grade 3 or 4	Immediately stop infusion and permanently discontinue cetuximab.
Dermatologic toxicities and infectious sequelae (e.g., acneiform rash,	First occurrence; grade 3 or 4	Delay infusion 1 to 2 weeks; if condition improves to grade ≤2, continue at 250 mg/m^2. If no improvement, discontinue cetuximab permanently.

Adverse reaction	Severity (CTCAE, version 5.0)	Dose modification
mucocutaneous disease)	Second occurrence; grade 3 or 4	Delay infusion 1 to 2 weeks; if condition improves to grade ≤2, continue at 200 mg/m^2. If no improvement, discontinue cetuximab permanently.
	Third occurrence; grade 3 or 4	Delay infusion 1 to 2 weeks; if condition improves to grade ≤2, continue at 150 mg/m^2. If no improvement, discontinue cetuximab permanently.
	Fourth occurrence; grade 3 or 4	Discontinue cetuximab permanently.
Pulmonary toxicity	Acute onset or worsening pulmonary symptoms	Delay infusion 1 to 2 weeks; if condition improves, continue at the dose that was being administered at the time of occurrence. If no improvement in 2 weeks or interstitial lung disease is confirmed, discontinue cetuximab permanently.
Ulcerative keratitis	Confirmed diagnosis	Interrupt or discontinue cetuximab permanently.

6.5.3 Clinical management of cytokine release syndrome

Symptoms of cytokine release will be managed as per Table 6.4 and according to local standard practice and in line with published guidelines.[22,23]

Recommendations for cytokine release syndrome management described in Table 6.4 can be modified by the individual study center as medically necessary or as appropriate without requiring a Protocol Amendment or being considered a Protocol deviation.

Table 6.4: Clinical management of cytokine release syndrome[24]

Grading assessment	Treatment
Grade 1 • Fever, constitutional symptoms	• Vigilant supportive care • Assess for infections

Grading assessment	Treatment
	(Treat fever and neutropenia if present, monitor fluid balance, antipyretics, analgesics as needed)
Grade 2 • Hypotension: responds to fluids or one low dose pressor • Hypoxia: responds to <40% O_2 • Organ toxicity: grade 2	***Extensive comorbidities or older age?*** → No: Vigilant supportive care (Monitor cardiac and other organ function closely) → Yes: Vigilant supportive care Tocilizumab* ± corticosteroids
Grade 3 • Hypotension: requires multiple pressors or high dose pressors • Hypoxia: requires ≥40% O_2 • Organ toxicity: grade 3, grade 4 transaminitis	• Vigilant supportive care • Tocilizumab* ± corticosteroids
Grade 4 • Mechanical ventilation • Organ toxicity: grade 4, excluding transaminitis	• Vigilant supportive care • Tocilizumab* ± corticosteroids

*Should be used if no other treatment option, only

6.5.4 Additional diagnostic measurements

Patients with pre-existing pulmonary diseases and patients taking concomitant chemotherapy known to be associated with interstitial lung disease (ILD) should be closely monitored. In the event of symptoms (such as dyspnoea, cough, fever) or radiographic findings suggestive of ILD, prompt diagnostic investigation should occur. If interstitial lung disease is diagnosed, cetuximab must be discontinued and the patient be treated appropriately.

Patients presenting with signs and symptoms suggestive of keratitis such as acute or worsening: eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmology specialist. If a diagnosis of ulcerative keratitis is confirmed, treatment with cetuximab should be interrupted or discontinued. If keratitis is diagnosed, the benefits and risks of continuing treatment should be carefully considered. Cetuximab should be used with caution in patients with a history of keratitis, ulcerative keratitis or severe dry eye. Contact lens use is also a risk factor for keratitis and ulceration.

6.6 Continued access to study intervention after the end of the study

Further supply of nanrilkefusp alfa beyond study completion will be ensured by the sponsor in case the investigator considers continued treatment with nanrilkefusp alfa as beneficial.

6.7 Treatment of overdose

For this study, an overdose of nanrilkefusp alfa will be defined as any dose above 13 µg/kg.

For this study, an overdose of cetuximab will be defined as any dose above 120% of the planned dose (i.e., 480 mg/m^2 for the initial dose and 300 mg/m^2 for subsequent doses).

No specific information is available on the treatment of overdose of nanrilkefusp alfa and/or cetuximab. In the event of overdose, the patient should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

6.8 Concomitant therapy

All treatments that the investigator considers necessary for a patient's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care.

All concomitant medication will be recorded on the electronic Case Report Form (eCRF) including all prescription and over-the-counter products, herbal supplements, and intravenous medications and fluids. If changes occur during the study period, documentation of drug dosage, frequency, route, and date should also be included on the eCRF.

All concomitant medications received from ICF signature to 90 days after the last dose of nanrilkefusp alfa and/or cetuximab (whichever occurs later) should be recorded. All concomitant medications administered during (S)AEs are to be recorded. SAEs are defined in section 8.3.1.2.

6.8.1 Rescue medication and supportive care

Patients should receive appropriate supportive care measures as deemed necessary by the treating investigator.

6.8.2 Prohibited medications

If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from study interventions may be required (also see section 7.1). The investigator is to discuss prohibited medication/vaccination with the sponsor's medical monitor. The final decision on any supportive therapy or vaccination rests with the investigator and/or the patient's primary physician. However, the decision to continue the patient on study interventions requires the mutual agreement of the investigator, the sponsor, and the patient.

Listed below are specific restrictions for concomitant therapy or vaccination during the course of the study:

- Concomitant use of drugs known to prolong the QT/QTc interval during the study should be avoided and only should be used if clinically indicated and in case of no other alternative. Some of the medications known to prolong the QT interval are:[25] amiodarone, azithromycin, ciprofloxacin, chlorpromazine, citalopram, domperidone, donepezil, escitalopram, fluconazole, haloperidol, levofloxacin, levomepromazine, methadone,

ondansetron, and sulpiride. A complete list of medications known to prolong the QT interval can be found at www.crediblemeds.org.

- Administration of live or live-attenuated vaccines within 30 days prior to the first dose of study interventions and within 90 days after the last dose of nanrilkefusp alfa and/or cetuximab, whichever is later, is prohibited. Note: Killed vaccines are allowed.
- Administration of another study intervention during treatment with nanrilkefusp alfa and cetuximab is prohibited.
- Another anti-cancer therapy during treatment with nanrilkefusp alfa and cetuximab is prohibited. Palliative radiotherapy of, e.g., painful bone metastases not defined as indicator lesions is allowed.

7 DISCONTINUATION OF STUDY INTERVENTION AND PATIENT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of study intervention

Discontinuation of study treatment does not represent withdrawal from the study.

A patient must be discontinued from study treatment for any of the following reasons:

- Confirmed radiographic disease progression as specified in section 10.2.7.
- Clinical disease progression (investigator's assessment)
- AE, namely intercurrent illness or study treatment-related toxicity that would, in the judgment of the investigator, affect assessments of the patient's clinical status to a significant degree or require discontinuation of study treatments
- Pregnancy of the patient
- Concomitant treatment with a prohibited medication
- Initiation of new systemic anti-cancer therapy
- Patient's decision
- Investigator's decision

After discontinuation of nanrilkefusp alfa and/or cetuximab (whichever occurs later), all patients will be followed up in the study as described in section 4.1.4.3.

If nanrilkefusp alfa needs to be stopped, patients will discontinue cetuximab as well. Such patients will receive standard of care treatment outside the clinical trial.

If cetuximab needs to be stopped due to an AE or the patient's or investigator's decision, nanrilkefusp alfa treatment can continue until any of the criteria for stopping or discontinuation of study treatment listed above is met. If cetuximab needs to be stopped for any of the reasons listed above except for an AE or the patient's or investigator's decision, nanrilkefusp alfa needs to be discontinued as well.

7.2 Patient discontinuation/withdrawal from the study

A patient may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons, or when the study is discontinued by the sponsor. This is expected to be uncommon. The patient will be permanently discontinued both from the study interventions and from the study at that time.

If the patient withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a patient withdraws from the study, s/he may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3 Lost to follow-up

A patient will be considered lost to follow-up if s/he repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the study.
- Before a patient is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, s/he will be considered to have withdrawn from the study.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the Schedule of activities. Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the patient should continue or discontinue study interventions.

Adherence to the study design requirements, including those specified in the Schedule of activities, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

RAS wild type at screening will be determined by using a locally performed FDA-approved test or an experienced local laboratory using validated test methods for the detection, based on tumor biopsy, or locally performed ctDNA assessment (including at least mutations in exon 2 [G12D, G12V, G12C, G12S, G12A, G12R, G13D]), determined by a laboratory using validated test methods. FDA-approved tests are listed here: https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools.

Procedures conducted as part of the patient's routine clinical management and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the Protocol-specified criteria and were performed within the time frame defined in the Schedule of activities.

8.1 Efficacy assessments

Throughout this section, the term "scan" refers to any medical imaging data used to assess tumor burden and may include cross-sectional imaging (such as CT or MRI), medical photography, or other methods as specified in this Protocol except ultrasound which unacceptable for efficacy assessments.

Scan evaluation by a local radiologist or by the investigator will be used for the main analyses. However, all scheduled scans for patients will be collected. In case of a deemed need for health authority interactions, a sensitivity analysis will be considered based on evaluation of imaging documentation by an independent review committee. A scan that is obtained at an unscheduled time point, for any reason (including suspicion of progression or other clinical reason), will also be collected if it shows disease progression, or if it is used to support a response assessment. In addition, historical scans that were obtained at disease progression on previous systemic anti-cancer treatment will be collected and may be qualified by an independent review committee.

The process for scan collection can be found in the site imaging manual. CT scans are preferred over other tumor imaging methods. For the abdomen and pelvis, contrast-enhanced MRI may be used when CT with iodinated contrast is contraindicated, or when mandated by local practice. The same type of scan should be used in a patient throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the assessment of response or progression based on imaging. Note: for the purposes

of assessing tumor scans, the term "investigator" refers to the local investigator at the site and/or the radiologist located at the site or at an offsite facility.

If brain scans are performed, magnetic resonance scans are preferred; however, CT scans are acceptable if MRI is medically contraindicated.

Bone metastases should be assessed using an adequate method (e.g., bone scans).

8.1.1 Initial tumor scans

Initial tumor scans must be performed within 21 days prior to ICF signature. The site study team must review screening scans to confirm the patient has measurable disease per RECIST 1.1.

If brain scans are performed to document the stability of existing metastases, the brain MRI should be acquired during screening. If MRI is medically contraindicated, CT with contrast is an acceptable alternative.

8.1.2 Tumor imaging during the study

The first on-study scan assessment should be performed at 6 weeks (±2 weeks; starting from cycle 1 day 1). Subsequent tumor scans should be performed every 6 weeks (±2 weeks).

All supplemental imaging must be collected.

Objective response should be confirmed by repeat scan performed at least 4 weeks after the first indication of a response is observed. Patients will then return to the regular scan scheduled, starting with the next scheduled time point. Patients who receive additional scans for confirmation do not need to undergo the next scheduled scan if it is fewer than 4 weeks later; scans may resume at the subsequent scheduled time point.

When radiological disease progression is identified by the investigator in clinically stable patients, disease progression is to be confirmed by another set of scans performed 4 to 8 weeks later, per iRECIST guidelines in section 8.1.5.

If disease progression is not confirmed, clinically stable patients are to continue study interventions until progression is confirmed. Patients are to return to their regular scan schedule. If the next scheduled scan will occur in less than 4 weeks, this scheduled scan may be skipped.

If disease progression is confirmed, study interventions will be discontinued. Exceptions are detailed in section 8.1.5.

8.1.3 End of treatment and follow-up tumor imaging

If patients discontinue study interventions, tumor scans should be performed at the time of discontinuation (±4-week window) unless previous scans were obtained within 4 weeks of discontinuation.

If patients discontinue study interventions without documented disease progression, every effort should be made to monitor disease status by acquiring tumor scans using the same schedule used while on treatment (every 6 weeks [±2 weeks]).

Scans are to be continued until:

- Confirmed disease progression per iRECIST

- Start of next-line anti-cancer treatment
- Pregnancy of the patient
- Withdrawal of consent by the patient
- End of the study

All imaging assessments need to have confirmatory imaging using the identical method after at least 4 weeks.

Patients who are clinically stable and treated past radiographic progression may continue to be assessed until progression is confirmed according to the rules of iRECIST, when clinically appropriate.

8.1.4 RECIST 1.1 assessment of disease

RECIST 1.1 will be used as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all Protocol guidelines related to disease status (e.g., discontinuation of study interventions).

8.1.5 iRECIST assessment of disease

iRECIST is based on RECIST 1.1 but adapted to account for the unique tumor response seen with immunotherapeutic drugs. iRECIST will be used by the investigator to assess tumor response and progression and make treatment decisions. When clinically stable, patients may continue study interventions beyond RECIST 1.1 progression with continued assessment of response according to the rules outlined in section 10.2. iRECIST reflects that some patients can have a transient tumor flare after the start of immunotherapy, then experience subsequent disease response. This data will be captured in the clinical database.

- If the patient is clinically stable, continue study interventions per Protocol
  - Perform scans 4 to 8 weeks after RECIST 1.1 progression
  - Continue investigator assessment per iRECIST
  - Collect scans
- If the patient is not clinically stable, best medical practice is to be applied

For the purpose of this decision process, lack of clinical stability is defined as:

- Unacceptable toxicity
- Clinical signs or symptoms indicating clinically significant disease progression
- Decline in performance status
- Rapid disease progression or threat to vital organs or critical anatomical sites (e.g., central nervous system metastasis, respiratory failure due to tumor compression, spinal cord compression) requiring urgent alternative medical intervention

8.2 Safety assessments

If patients feel unwell at any point in time during the study after being discharged from the hospital, they should contact their study investigator as indicated in the ICF.

8.2.1 Physical examinations, ECOG performance status, body height, and body weight

General physical examination with organ/system-specific physical examination will be carried out by a licensed physician (or the physician's assistant or a nurse practitioner).

For screening, a complete physical examination will be performed including head (eyes, ear, nose, and throat), neck, cardiovascular, chest/lungs, abdomen (including liver and spleen size), extremities, neurological, skin, and lymph nodes. For subsequent visits, a physical examination is to be done with the focus on abdomen (including liver and spleen size), lymph nodes, and any other system that may contribute to clinical disease assessments.

An ECOG performance status will be assigned, and body height and body weight will be measured.

8.2.2 Vital signs

Vital signs will include blood pressure (systolic and diastolic, after ≥5 minutes of rest), body temperature, and heart rate.

8.2.3 Special assessments on treatment days

8.2.3.1 Nanrilkefusp alfa treatment days of cycles 1 to 3

Patients will be observed in the hospital up to 4 hours following nanrilkefusp alfa administration. Vital signs (blood pressure [systolic and diastolic, after ≥5 minutes of rest], body temperature, and heart rate) will be documented at the following frequency until discharge:

- Before nanrilkefusp alfa administration
- 15 minutes (±5 minutes) after nanrilkefusp alfa administration
- 30 minutes (±5 minutes) after nanrilkefusp alfa administration
- 2 hours (±15 minutes) after nanrilkefusp alfa administration
- 4 hours (±30 minutes) after nanrilkefusp alfa administration

8.2.3.2 Nanrilkefusp alfa treatment days of cycle 4 and onwards

Patients will be observed in the hospital up to 2 hours after nanrilkefusp alfa administration. Vital signs (blood pressure [systolic and diastolic, after ≥5 minutes of rest], body temperature, and heart rate) will be documented at the following frequency until discharge:

- Before nanrilkefusp alfa administration
- 15 minutes (±5 minutes) after nanrilkefusp alfa administration
- 30 minutes (±5 minutes) after nanrilkefusp alfa administration
- 2 hours (±15 minutes) after nanrilkefusp alfa administration

8.2.4 Electrocardiography and left ventricular ejection fraction

Standard 12-lead ECG will be done locally. Left ventricular ejection fraction will be assessed using either echocardiography or nuclear medicine methodology.

8.2.5 Clinical safety laboratory assessments

Clinical safety laboratory assessments are to be performed by a local laboratory. Sample collection, handling, storage, and shipment of samples will be performed according to local laboratory standards.

8.2.5.1 Coagulation

Coagulation tests will include prothrombin time, activated partial thromboplastin time, international normalized ratio, D-dimer, and fibrinogen.

8.2.5.2 Hematology

Hematology tests will include hemoglobin, glycated hemoglobin at screening, hematocrit, red blood cell count, reticulocytes, white blood cell count (with full differentiation), absolute lymphocyte count, and platelet count.

8.2.5.3 Biochemistry

Blood biochemistry tests will include Na, K, Cl, phosphate, Mg, Ca, albumin, total protein, ALT, AST, bilirubin (direct, total), alkaline phosphatase, lactate dehydrogenase, creatinine clearance calculated by the Cockcroft-Gault formula, creatinine, glucose (preferably fasting), urea or blood urea nitrogen, cholesterol, triglyceride, C-reactive protein, uric acid, amylase, and lipase.

8.2.5.4 Urinalysis

The following parameters are to be analyzed: pH, glucose, protein, bilirubin, urobilinogen. Microscopic examination (mandated only if clinically indicated): red blood cell count, white blood cell count, epithelial cells, bacteria.

8.2.5.5 Serology testing for infections

Serology testing for infections will include testing for HIV, HBV, and HCV.

8.2.6 Pregnancy testing

WOCBP will be tested for pregnancy.

8.3 AEs, SAEs, and other safety reporting

8.3.1 Definitions

8.3.1.1 AEs

International Council for Harmonisation (ICH) guideline E2A defines an AE as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (e.g., tachycardia, enlarged liver), symptom (e.g., nausea, chest pain), abnormal result of an investigation (e.g., laboratory finding), or disease temporarily associated with the use of a medicinal product, whether or not considered related to the medicinal product.

According to the US FDA (21CFR312.32), an AE means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

8.3.1.2 SAEs

A SAE is any untoward medical occurrence that at any dose fulfills one or more of the following criteria:

- Results in death
- Is immediately life-threatening

  The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Requires inpatient hospitalization or prolongation of existing hospitalization

  A hospitalization is defined as an inpatient overnight stay, but this can be shorter than 24 hours.
- Is another medically significant event defined as an event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent any of the above listed outcomes

8.3.1.3 Excluded events

Hospitalization for the following reasons will not be regarded as serious (not immediately reportable):

- Routine treatment or monitoring of the disease under study, including hospitalization due to study-related procedures, not associated with any deterioration of the patient's status
- Elective or pre-planned treatment (before signing the ICF) for a pre-existing condition that is unrelated to the disease under study and has not worsened since signing the ICF
- Social reasons, respite care, and in the absence of a medical condition (e.g., for observational purposes without any intervention)

8.3.1.4 Severity/intensity vs. seriousness

ICH E2A: The term "severe" is often used to describe the intensity (severity) of a specific event (as mild, moderate, or severe myocardial infarction); the event itself, however, may be of a relatively minor medical significance (such as a severe headache). This is not the same as "serious", which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

8.3.2 Time period and frequency for collecting AE, SAE, and other reportable safety event information

Every effort should be taken to collect all AEs and SAEs from the date of the patient's signing the ICF until 90 days after the last dose of nanrilkefusp alfa and/or cetuximab (whichever occurs later).

Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately to the sponsor or designee if the event is considered as having a suspected causal relationship to nanrilkefusp alfa and/or cetuximab per the investigator's judgment.

Pregnancies of the patient or patient's female partner must be reported from the date of the patient's signing the ICF to 60 days after the last dose of cetuximab or 30 days after the last dose of nanrilkefusp alfa, whichever is later.

8.3.3 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrences. A standardized question such as "Have you had any health problems since your last visit or since you were last questioned?" will be given by the investigator or the investigational site personnel at each contact with the patient.

The investigator assesses at each visit (or more frequently, if necessary) if there are any changes in AE diagnosis, severity, suspected causal relationship to clinical trial medication/procedure, interventions required to treat the event, and AE outcome.

8.3.4 Follow-up of AEs and SAEs

After the initial (S)AE report, the investigator is required to proactively follow each patient at subsequent visits/contacts (or more frequently, if necessary).

AEs are monitored (followed up) until resolution or until 90 days after the last dose of nanrilkefusp alfa and/or cetuximab, whichever is later.

All SAEs will be followed until resolution, stabilization (becoming a permanent condition), or the patient is lost to follow-up as defined in section 7.3.

8.3.5 Regulatory reporting requirements for SAEs

Prompt notification by the investigator to the sponsor or designee of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of nanrilkefusp alfa are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of an investigational product under clinical investigation. The sponsor or designee will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC (in the US)/EC (in the EU), and investigators.

An investigator who receives an expedited or periodic safety report (e.g., suspected unexpected serious adverse reaction report, summary or line listing of suspected unexpected serious adverse reactions) or other specific safety information from the sponsor or designee will review

and then file it along with the IB and will notify the IRB/IEC (in the US)/EC (in the EU), if appropriate according to local requirements.

8.3.6 Pregnancy

Pregnancy is not considered an (S)AE unless it meets any criteria for becoming serious (see SAE definitions in section 8.3.1.2). Patients must inform the investigator of any newly identified pregnancy or pregnancy of their partners without delay.

If a patient inadvertently becomes pregnant while on treatment with nanrilkefusp alfa and/or cetuximab, the patient will be immediately discontinued from study interventions (see section 7.1).

Pregnancies will be monitored by the investigator to determine the outcome, including spontaneous abortion or voluntary termination, birth details, and the presence or absence of any birth defects, congenital abnormalities, or maternal or newborn complications. Every infant has to be followed up for 2 months after delivery.

Consent to report information on the outcome of the pregnancy of male patients' partners needs to be obtained from the pregnant partners.

8.3.7 Assessing AEs

Information about adverse reactions (causally related events) already known for the investigational medicinal products can be found in the IB and Erbitux's current package insert/US prescribing information (for the US)[17] and current SmPC (for the EU)[18] or will be communicated between IB updates in the form of "Dear Investigator Letter".

8.3.7.1 Causality

The investigator needs to assess the causal relationship of any AE to:

- Nanrilkefusp alfa
- Cetuximab
- Other suspected cause(s) of the event (e.g., concurrent disease, concomitant medication)

This assessment is based on the investigator's clinical judgment, taking into account all relevant information available at the time of AE reporting including (but not limited to):

- Temporal association of the event onset with administration of the medication/procedure
- Known type of reaction for any of the administered drugs
- Disappearance or abating of symptoms when the drug is discontinued or the dose is reduced
- Reappearance of symptoms when the drug is re-administered
- Event may or may not be caused by the patient's health condition
- Presence of risks or factors not related to study interventions that are known to be associated with the occurrence of the event

Causal relationship of all AEs will be classified as follows:

- **Not suspected**: it is not plausible that the AE is caused by medication/procedure and a likely alternative explanation exists.

No reasonable possibility of a causal or temporal relationship.

- **Suspected**: it is plausible that the AE is caused by medication/procedure.

  Reasonable possibility of a causal relationship.

*For the purposes of safety reporting, **"reasonable possibility"** means there is evidence to suggest a causal relationship between one of the drugs/procedure and the AE.*

8.3.7.2 Severity/intensity

Severity or intensity of an AE has to be assessed according to the National Cancer Institute's CTCAE, version 5.0. A grading scale is provided for AE terms displaying grades 1 through 5 with unique clinical descriptions of severity for each AE.

Grading refers to the severity of the AE.

8.3.8 Reporting by the investigational site

8.3.8.1 AEs

Any AE, whether or not considered to be causally related to the trial medication and regardless of its seriousness, must be reported (described and recorded) in the AE section of the patient's eCRF on an ongoing basis. Each AE will be evaluated by the investigator to determine its term and grade according to the CTCAE, version 5.0. In case a suitable CTCAE term is not available, an appropriate medical verbatim term may be used instead.

Only clinically relevant abnormal laboratory values, vital signs, or examination abnormalities need to be documented as AEs. Whenever possible, a diagnosis rather than symptoms should be provided on the AE eCRF page (e.g., anemia instead of low hemoglobin).

Clinically relevant here means: induce clinical signs or symptoms, require therapy (e.g., hematologic abnormality requiring treatment), require a change in trial medication(s), or require a change in the clinical trial schedule or per investigator's discretion.

Physical examination findings will be compared with the baseline status and any significant change, as assessed by the investigator, must be documented as an AE.

A surgical procedure is not an AE but a therapeutic measure for a condition that necessitates surgery. Therefore, the condition for which the surgery is required has to be reported as an AE.

Any pre-planned surgery (i.e., planned before signature of the ICF) or other intervention permitted by this study Protocol and the condition leading to that measure are not AEs. In such cases, the underlying condition needs to be documented in the patient's medical history on the eCRF.

Death itself is not an AE term but the outcome of an event, which needs to be described using medical terminology. Information about death will be captured on the respective eCRF page along with relevant details (date of death, immediate and underlying causes of death).

8.3.8.2 Documenting on eCRFs

The reported term should be a medical diagnosis or sign/symptom of the event, not a procedure. Each symptom in a constellation of symptoms should be listed separately if the investigator has not set a diagnosis.

Fluctuations or re-occurrences of a condition, which are considered normal for the patient and are recorded on the patient's eCRF medical history, do not need to be reported as an AE. However, if the condition deteriorates during the trial, it needs to be captured as an AE.

If the same AE occurs repeatedly, it must be assessed and documented separately each time.

If possible, each AE should be evaluated to determine:

- Event term (per CTCAE, version 5.0) or a description of the AE in medical terms (not as reported by the patient)
- Severity grade or intensity of the event as assessed by the investigator (1-5 per CTCAE, version 5.0)
- Its causal relationship to nanrilkefusp alfa and cetuximab, as assessed by the investigator (suspected; not suspected)
- Other suspected cause(s) of the event (e.g., concurrent disease, concomitant medication)
- Event duration, including onset date and end date
- Action taken with nanrilkefusp alfa and cetuximab due to the reported event
- Event seriousness (non-serious or serious AE)
- Event outcome

8.3.8.3 Immediately reportable events

The investigator or any investigational site staff must immediately (**within 24 hours of awareness at the latest**) notify/report to the sponsor or designee any initial or medically relevant follow-up information about these events:

- SAE
- Pregnancy of the patient or patient's female partner

The initial notification can be done over the phone on +420 725 385 443. This notification must be followed within an additional 24 hours by a written report (i.e., a completed SAE Report Form or Pregnancy Data Collection Form), providing all available information and a detailed narrative description. A formless notification (without a report form) is not required if the initial/follow-up information is reported on the appropriate form within 24 hours of knowledge.

The investigator must not wait to receive additional information to fully document the event before notifying the sponsor or designee **primarily via the eCRF system**; or via:

Email: safety@sotio.com

Fax: +420 224 175 498

Phone: +420 725 385 443

Follow-up information must be sent within the same timelines using the same contact details as outlined above.

Additionally, refer to the safety reporting instructions for sites for information on how to report these events.

Minimum notification/reporting requirements

The following information must be provided for a valid notification/report:

1. Identification of the notifying/reporting person (e.g., name of the reporter)
2. Identification of the patient (e.g., patient number)
3. Concerned study treatment(s) (nanrilkefusp alfa and/or cetuximab) or clinical trial (e.g., SC105 or AURELIO-05)
4. Reason for notification/reporting (i.e., SAE or pregnancy of the patient or patient's female partner)
5. Event term

*In addition, providing the **assessment of the causal relationship** is necessary for comprehensive evaluation by the sponsor and potential regulatory submission.*

8.3.8.4 Report forms

The SAE Report Form, **primarily completed within the eCRF system** for the study, will be used for reporting of SAEs and submitted to the sponsor or designee. In case the eCRF system is not available/accessible, a paper SAE Report Form is filled out and sent to the sponsor or designee (see details above).

For reporting of pregnancies, the paper Pregnancy Data Collection Form is to be used. Completion guidelines provide information on format and details of the information required.

Originals of the paper report forms must be kept in the site study file.

The report forms need to be completed in English.

All immediately reportable events from the investigational site to the sponsor or designee (i.e., SAEs and patients' or partners' pregnancies) must also be recorded in the site's source documentation and on the eCRF as appropriate.

8.4 PK

The following serum PK parameters will be determined (nanrilkefusp alfa and cetuximab; cetuximab samples will be collected to be analyzed later during the course of the study if needed):

- Area under the concentration-time curve (AUC; over the last measurable timepoint [AUC_{last}], extrapolated to infinity [AUC_{inf}] and over the dosing interval [AUC_{tau}])
- Observed maximum concentration (C_{max})
- Time to maximum concentration (T_{max})
- Pre-dose concentration (C_{trough})
- Apparent terminal elimination half-life ($T_{1/2}$)

- Apparent systemic clearance (CL) for single dose and steady state
- Apparent volume of distribution at steady state (V_{ss}) and during terminal phase (V_z)
- Accumulation ratio (R_{AUC}, R_{Cmax})

PK parameters will be generated by noncompartmental and/or compartmental approaches as appropriate. Additional PK parameters may be calculated at the discretion of the pharmacokineticist. Further details will be specified in the PK analysis plan.

The actual date and time (24-hour clock time) of each sample will be recorded.

Instructions on sample collection, handling, storage, and shipment of samples are detailed in the study-specific laboratory manual provided to the study site.

8.5 Genetics

Participation in genetic research is optional. Patients who do not wish to participate in the genetic research may still participate in the study.

Genetic research will include circulating tumor DNA analysis, assessment of Fc gamma receptor polymorphism, and presence and changes in T-cell clonality.

Instructions on sample collection, handling, storage, and shipment of samples are detailed in the study-specific laboratory manual provided to the study site.

8.6 Biomarkers

Translational research may be conducted as appropriate including but not limited to the assessment of 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 DNA at screening and following nanrilkefusp alfa and cetuximab treatment.

The correlation/relationship between biomarkers and measures of clinical efficacy, safety, pharmacodynamic activity, and/or mechanism of action will be evaluated.

DNA analyses are optional. Patients who do not wish to participate in this research may still participate in the study (also see section 8.5).

Instructions on sample collection, handling, storage, and shipment of samples are detailed in the study-specific laboratory manual provided to the study site.

Samples may be stored for a maximum of 20 years (or according to local regulations) after the end of the study at a facility selected by the sponsor to enable further analyses of biomarker responses to nanrilkefusp alfa in combination with cetuximab.

EGFR mutational status and expression will be determined from the collected whole blood samples.

8.7 Immunogenicity assessments

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.

Samples for cetuximab ADAs will be collected. These samples will be stored and a decision about their analysis will be taken at a later date.

Instructions on sample collection, handling, storage, and shipment of samples is detailed in the study-specific laboratory manual provided to the study site.

Samples may be stored for a maximum of 20 years (or according to local regulations) after the end of the study at a facility selected by the sponsor to enable further analysis of immune responses to nanrilkefusp alfa in combination with cetuximab.

8.8 Health economics

Health economics parameters will not be evaluated in this study.

8.9 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical hypotheses

No formal testing of statistical hypotheses is planned in this open-label, single-arm trial.

The primary objective is to estimate the antitumor efficacy of nanrilkefusp alfa in combination with cetuximab according to RECIST 1.1 by means of ORR. Other efficacy endpoints (e.g., iORR, [i]BOR, [i]PFS) will also be explored to further evaluate the antitumor efficacy of the combination therapy.

9.2 Analysis sets

9.2.1 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.

9.2.2 PK population

The PK population will consist of all patients who are PK evaluable.

9.2.3 Efficacy population

The efficacy population will consist of all patients exposed to the combination therapy for at least one treatment cycle.

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

9.2.4 Per Protocol population

The per Protocol (PP) population is defined as all patients who had at least one full treatment cycle of nanrilkefusp alfa and cetuximab, did not violate any eligibility criteria, and did not have any relevant major Protocol deviations.

9.3 Statistical analyses

9.3.1 General considerations

Analyses will be descriptive (i.e., without a comparison). Safety will be analyzed as described in section 9.3.3.2.

Summary statistics will include:

- Counts and percentages (categorical data)
- Number of observations, mean, standard deviation, median, minimum, and maximum (continuous data)

The ORR, iORR, BOR, iBOR, CBR, and iCBR will use the exact method based on the binomial distribution[26] to derive 95% confidence intervals (CIs). Kaplan-Meier estimations and

estimations of median (if reached) with log-log 95% CI, Q1 (25th percentile), and Q3 (75th percentile) will be used for DoR, iDoR, PFS, iPFS, TtR, iTtR, TtP, iTtP, PFS2, and OS. 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.

The last value of CT scan or MRI on or up to 21 days before the date of the first study treatment will be used as the baseline value for each assessment. 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.

9.3.2 Primary endpoint 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 and presented as a point estimate and a 95% CI. Patients with missing data will be considered as non-responders.

Sensitivity analyses will include the use of:

- ASaT and PP populations
- No imputation of missing data

9.3.3 Secondary endpoints analysis

9.3.3.1 Efficacy endpoints

- iORR

The iORR is defined as the proportion of patients with complete response according to iRECIST (iCR) or partial response according to iRECIST (iPR) and will be analyzed and presented as a point estimate and a 95% CI. Patients with missing data will be considered as non-responders.

- BOR and iBOR

The BOR and iBOR are defined as the best response from the start of study treatment until progression of disease or death and will be summarized with counts and percentages together with a 95% CI. Stable disease according to RECIST 1.1 (SD) and stable disease according to iRECIST (iSD) needs to last at least 6 weeks from the baseline scan; if not, at least one follow-up scan is required to declare stable disease.

- DoR and iDoR

The DoR and iDoR are defined as the time until progression of disease for patients with partial response (PR, iPR) or complete response (CR, iCR) and will be summarized using Kaplan-Meier estimates. Responders will be considered to have an ongoing response if they: i) have not progressed, and ii) have not started a next-line anti-cancer therapy, and iii) have not been lost to follow-up, and iv) are alive.

Patients with missing data will be censored/considered as having an event as specified in Table 9.1.

Table 9.1: 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

- CBR and iCBR

The CBR and iCBR are defined as the number of partial responses (PR, iPR), complete responses (CR, iCR), and stable diseases (SD, iSD) and will be analyzed and presented as a point estimate and a 95% CI. Stable disease (SD, iSD) needs to last at least 6 weeks from the baseline scan; if not, at least one follow-up scan is required to declare stable disease. Patients with missing data will be considered as non-responders.

- 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.

Patients with missing data will be censored/considered as having an event as specified in Table 9.2.

Table 9.2: PFS and iPFS events and censoring

Situation	Date of progression or censoring	Outcome
Incomplete or no baseline tumor assessment.	Date of 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

Situation	Date of progression or censoring	Outcome
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

- TtR and iTtR

TtR and iTtR are defined as the time from the first day of study treatment until the first date of partial response (PR, iPR) or complete response (CR, iCR) and will be summarized using Kaplan-Meier estimates. 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.

- 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.

Patients with missing data will be censored/considered as having an event as specified in Table 9.3.

Table 9.3: TtP and iTtP events and censoring

Situation	Date of progression or censoring	Outcome
Incomplete or no baseline tumor assessment.	Date of 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

Situation	Date of progression or censoring	Outcome
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

9.3.3.2 Safety endpoints

- DLTs

The incidence of DLTs (in DLT-evaluable patients, see section 4.1.3) by dose level will be summarized with counts and percentages.

- TEAEs

A TEAE is defined as an AE that started or worsened at or after the start of study treatment.

TEAEs will be summarized with counts and percentages. These will be provided for the incidence of, but not limited to: any TEAE, any serious TEAE, any grade 3-5 TEAE, any drug-related TEAE, any serious and drug-related TEAE, any grade 3-5 and drug-related TEAE, temporarily discontinued due to a TEAE, permanently discontinued due to a TEAE, death. TEAE incidence frequencies by system organ class and preferred term will also be provided.

- Safety laboratory findings and vital signs

Safety laboratory findings and vital signs measurements will be summarized accordingly (if categorical or continuous data). Laboratory results will be summarized using SI units as appropriate.

Further details on analyses to be performed will be specified in the final statistical analysis plan (SAP).

9.3.4 Exploratory endpoint analysis

- PFS on next-line anti-cancer treatment (PFS2)

PFS2 is defined as the time from the first day of study treatment until the date of second radiological disease progression (i.e., progression on next-line anti-cancer treatment) or death and will be summarized using Kaplan-Meier estimates.

Patients with missing data (i.e., without second radiological disease progression) will be censored at the last time known to be alive.

- 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. Patients with missing data will be censored at the last time known to be alive.

9.3.5 Other analyses

Other sensitivity, secondary, and exploratory analyses such as PK, immunogenicity, biomarker exploratory analyses, and circulating tumor DNA will be described in the final SAP.

9.4 Interim analysis

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.

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[26] 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:

1. lower than the minimal ORR, and
2. 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%[21]; 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.

9.5 Sample size determination

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 (see section 9.2.3) 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 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%[21]
- Minimal ORR (relative increase, absolute increase): 28.8% (1.44, 8.8%)
- Desired ORR (relative increase, absolute increase): 36.8% (1.84, 16.8%)

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, ethical, and study oversight considerations

10.1.1 Regulatory and ethical considerations

The Protocol, ICF, and appropriate related documents must be reviewed and approved by an IRB/IEC (in the US)/EC (in the EU) constituted and functioning in accordance with ICH Guideline E6 Good Clinical Practice (GCP)[27] and any local regulations, and by the competent authority (CA). Any Protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC (in the US)/EC (in the EU) and to the CA for review and approval, except for changes involving only logistical or administrative aspects of the study (e.g., change of clinical research associates [CRAs], change of telephone numbers). Documentation of IRB/IEC (in the US)/EC (in the EU) compliance with ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

A signed letter of study approval from the IRB/IEC (in the US)/EC (in the EU) chairman must be sent to the principal investigator or, if regionally required, the head of the medical institution with a copy to the sponsor before study start and the release of study interventions to the site by the sponsor or its designee. If the IRB/IEC (in the US)/EC (in the EU) decides to suspend or terminate the study, the investigator (or if regionally required, the head of the medical institution) will immediately send the notice of study suspension or termination by the IRB/IEC (in the US)/EC (in the EU) to the sponsor.

Study progress is to be reported to IRBs/IECs (in the US)/ECs (in the EU) and to CAs annually (or as required) by the investigator or sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB/IEC (in the US)/EC (in the EU), s/he will forward a copy to the sponsor at the time of each periodic report.

The investigator(s) or the sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC (in the US)/EC (in the EU) (or if regionally required, the investigator and the relevant IRB/IEC (in the US)/EC (in the EU) via the head of the medical institution) and the CA of any reportable AEs per ICH guidelines and local IRB/IEC (in the US)/EC (in the EU) standards of practice. Upon completion of the study, the investigator or sponsor will provide the IRBs/IECs (in the US)/ECs (in the EU) and the CAs with a brief report of the outcome of the study, if required.

At the end of the study, the sponsor should notify the IRBs/IECs (in the US)/ECs (in the EU) and CAs as regionally required.

This study will be conducted in accordance with standard operating procedures of the sponsor (or designee), which are designed to ensure adherence to applicable regulatory requirements, and in accordance with the current version of the Declaration of Helsinki and ICH guidelines on GCP.

10.1.2 Financial disclosure

Information on potential financial interests will be provided by all participating investigators. This information will be collected by the sponsor (or a delegated party) before the initiation of the clinical trial, during the course of the clinical trial whenever the financial interests may change, and for a period of one year after the completion of the clinical trial, or termination of a particular individual's participation in this trial.

10.1.3 Informed consent process

10.1.3.1 Clinical trial participation

Written informed consent will be given by each patient before any procedure of this clinical trial is performed. The process of obtaining the informed consent must comply with applicable ICH GCP E6 guidelines as implemented in EU guidelines and national regulatory requirements.

It is the responsibility of the investigator that patients are clearly and fully informed about the purpose of the clinical trial, its potential risks and benefits, and other critical issues regarding the clinical trial, in which the patient volunteers to participate, before undergoing any clinical trial-specific procedure.

The IRB/IEC- (in the US)/EC- (in the EU) approved written ICF, which complies with the above-mentioned regulations, will be provided to each patient. The patient should be given ample time to read and to understand the ICF, and to get the answers to any enquiry related to the clinical trial s/he may have. The ICF should be signed personally by the patient and subsequently by the delegated investigator who obtains the consent. The patient will be provided with a fully signed ICF printout, and with any other written information, before the participation in the clinical trial.

The process of obtaining informed consent should be documented in the patient's source documents.

The sponsor will provide the investigator with a master ICF that complies with ICH GCP guidelines and regulatory requirements and is considered appropriate for this clinical trial. Any changes to this master ICF suggested by the investigator must be agreed to by the sponsor before being submitted to the IRB/IEC (in the US)/EC (in the EU). A copy of the approved version, together with all accompanying approvals, must be provided to the sponsor.

The ICF and any other information provided to patients are subject to changes and revisions whenever important new information relevant to patients' willingness to continue participation in the clinical trial becomes available. Once the IRB/IEC (in the US)/EC (in the EU) approval/favorable opinion on this new information is obtained, the delegated investigator should inform each patient about this newly emerging information as soon as possible. All procedures and regulations to be followed and mentioned above apply also to this scenario, and this process should also be documented in the patient's source documents.

10.1.3.2 Pharmacogenomic research

Patients will be asked to participate in pharmacogenomic research (see sections 8.5 and 8.6). Depending on local laws and regulations, the patients might be required to provide their written consent to this research by signing a separate ICF. In such a case, the consent to participate in the pharmacogenomic research will be optional and not a prerequisite for entry into the clinical trial.

10.1.4 Data protection

In order to ensure that personal information of each patient is kept confidential and protected, names and any other information that allow direct identification of a patient will not be on the eCRFs or included in any records or samples provided to the sponsor or sponsor's authorized representatives; such information will be pseudonymized, i.e., all such information will be

replaced by a specific code (patient number) assigned by a study doctor and all patients will be identified on eCRFs or any other records or samples by a patient number only.

The personal information collected for the purposes of this study will be held by the study sites, the sponsor and sponsor's authorized representatives, which together are responsible for processing of personal information in accordance with the applicable data protection laws, including the Swiss Data Protection Act, the Swiss revised Data Protection Act, the General Data Protection Regulation (EU) 2016/679, and any corresponding local legislation.

The sponsor and its authorized representatives will analyze and use the personal information they receive for the purposes of this study only. These include:

- checking patients' suitability to take part in the study,
- monitoring patients' health during treatment with nanrilkefusp alfa in combination with cetuximab,
- comparing and pooling study results,
- establishing whether nanrilkefusp alfa in combination with cetuximab meets the appropriate standards of safety set by the authorities,
- establishing whether nanrilkefusp alfa in combination with cetuximab is effective,
- supporting the clinical development of nanrilkefusp alfa in combination with cetuximab,
- supporting the licensing application for regulatory approval of nanrilkefusp alfa in combination with cetuximab anywhere in the world,
- supporting the marketing, distribution, sale, and use of nanrilkefusp alfa in combination with cetuximab anywhere in the world,
- complying with specific regulations governing clinical trials.

Participation of patients in this study is voluntary and they may withdraw from the study at any time by informing the investigator. Their participation in the study will then end and the study personnel will stop collecting personal information from the patients, but the sponsor will need to retain and use the pseudonymized personal information and associated research results that have already been collected from the patient. The sponsor must do this to comply with its legal and regulatory obligations, to maintain the scientific integrity of the study, and to complete the marketing authorization process for nanrilkefusp alfa in combination with cetuximab. It may be necessary to retain certain aspects of pseudonymized (coded) personal information for at least 25 years following the end of the study to comply with applicable laws and regulatory requirements and to ensure the scientific integrity of the study.

If necessary for the study purposes mentioned above, the sponsor may communicate such pseudonymized personal information to third parties (such as service providers, contractors, and research institutions that support the study) and regulatory or other governmental agencies that need to check the results of the study.

These third parties may be located in countries of the European Economic Area (EEA), in Switzerland, in the United States, and in other countries that are outside of the EEA. Some non-EEA countries may not offer the same level of privacy protection. However, the sponsor will keep personal information it receives as confidential as possible within the limits of the law. The sponsor will implement appropriate contractual measures, including the standard data

protection contractual clauses, to ensure that the relevant recipients outside the EEA provide an adequate level of protection to personal information as set out in this form and as required by applicable law.

The sponsor, either alone or together with other researchers, may publish or present the results of the study; however, personal information will not be disclosed in any publication or presentation.

All persons have certain rights to gain access to and correct any inaccuracies in the personal information held about them. In certain circumstances, they can also request restriction of processing of their personal information, object to certain types of processing of their personal information, request their personal information be erased and have their personal information provided to them or a third party in a digital format. The sponsor shall comply with the above requests to the fullest extent consistent with other legal and regulatory obligations and where required by law.

Personal data cannot be erased, even after patients finish or terminate their participation in the study, in order to guarantee the validity of the clinical research and to comply with statutory duties and drug authorization requirements.

Representatives from government agencies, the local EC and sponsor or its authorized representatives may also need access to medical records and study records for the purpose of checking data collected for the study.

The sponsor shall process all personal information of the patients in the study in accordance with the applicable data protection laws, including the Swiss Data Protection Act, the Swiss revised Data Protection Act, the General Data Protection Regulation (EU) 2016/679, any applicable local legislation, and the internal data protection policies reflecting organizational and technical arrangements to avoid unauthorized access, disclosure, dissemination, alteration, or loss of information and personal data processed. The organizational and technical measures introduced by the sponsor in relation to protection of personal information of the patients involve the above mentioned pseudonymization of personal information, appropriate controls to restrict its employees access to the personal information, a physical access control to any premises where the personal information is stored, an electronic access and system control logging for any systems containing personal information, data entry and data transfer control, availability control (back-up and recovery concept), network protection including firewalls and penetration testing procedures for regular testing, industry-standard security policies and procedures including assessment and evaluation of processes and regular training procedures. In the event of any security breach, the incident management procedures would be implemented, and the sponsor would notify such breach as applicable.

10.1.5 Organizational structure of the study

The sponsor of the clinical trial, SOTIO, may delegate certain tasks to designees, e.g., a contract research organization (CRO) or other third-party vendors. A list of such designated collaborators, including their contact details, will be documented in the investigator's manuals/Investigator Site File.

10.1.6 Dissemination of clinical study data

By signing the Protocol, every participating investigator agrees to keep all information and results concerning the clinical trial and the investigational product strictly confidential. The confidentiality obligation also applies to all personnel involved at the investigational site.

10.1.7 Data quality assurance

An eCRF is required and must be completed for each patient by qualified and authorized personnel. All data on the eCRF must reflect the corresponding source document. Any correction to entries made on the eCRF must be documented in a valid audit trail where the correction is dated, the individual making the correction is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the Protocol for the purposes of the study should be collected. The investigator must sign the eCRFs.

10.1.8 Trial monitoring, access to source documentation, and data retention

Before trial initiation, at the investigators' meeting or during the Site initiation visit, a representative of the sponsor or a CRO will review the Protocol and eCRFs with the site staff. During the clinical trial, the CRA will oversee the progress of the clinical trial and will visit the site regularly to verify the completeness of patient records, reliability and accuracy of entries on eCRFs, the site's adherence to the Protocol and GCP, the progress of enrollment, and that study interventions are being stored, dispensed, and accounted for according to specifications. The CRA will also ensure that the safety and rights of the patients are not compromised. Key clinical trial personnel must be available to assist the CRA during these visits.

For each patient recruited into the clinical trial, the investigator must maintain source documents, which should consist of case and visit notes (hospital or outpatient clinic medical records) containing demographic and medical information, laboratory data, and results of any other tests or assessments. All information on eCRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original of the ICF signed by the patient (the second signed original must be given to the patient).

The investigator must allow the CRAs or other delegated representatives to visit all site locations, and to allow direct access to all clinical trial-related documentation and data, as well as to the patient's source documents and other charts and records.

Monitoring standards of the sponsor require full verification for the presence of a fully signed and dated ICF, adherence to the inclusion/exclusion criteria, documentation of SAEs, and recording of data that will be used for all primary and safety variables. Additional verification of the consistency of the source data with the eCRFs will be performed according to a clinical trial-specific monitoring plan.

Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

The sponsor assumes accountability for actions delegated to other individuals (e.g., CROs).

The trial may also be evaluated by any other designee delegated by the sponsor, IRB/IEC (in the US)/EC (in the EU) representatives, or by any independent institutional or government inspectors, who must be given direct access to the same as mentioned above. Such a possibility must also be clearly mentioned in the patient's ICF.

The investigator must promptly notify the sponsor or its delegated representatives any time the request for inspection is raised by any regulatory agency, and to provide copies of all documentation received from such an agency.

The investigator or institution must retain all trial-related records, materials provided by the sponsor or its delegated collaborators, copies of eCRFs, and source documents of patients for a specified period of time. This period of time is derived from the locally applicable regulation guidelines or requirements, institution procedures, or requirements stipulated by the sponsor or its representatives, whichever is longer.

It is requested that at the completion of the required retention period, or should the investigator retire or relocate, the investigator contact the sponsor, allowing the sponsor the option of permanently retaining the study records.

10.1.9 Study and site start and closure

The first act of recruitment is the signature of the ICF by the first patient enrolled and will be the study start date.

The end of the study is defined in section 4.4.

10.1.10 Publication policy

The results of this clinical trial will be published and/or presented at scientific meetings in their totality in a timely manner. Any formal publication of clinical trial results will be a collaborative effort between the sponsor and the investigator(s). All manuscripts or abstracts will be reviewed and approved in written by the sponsor before submission. The sponsor may request a delay in publication if there are important intellectual property concerns but does not have the right to suppress the publication of the clinical trial results indefinitely.

Authorship will be determined by mutual agreement, with the coordinating investigator of this clinical trial being given priority for first authorship. Publications will include all clinical trial investigators in the order of their relative patient contribution, taking into account also contributions during Protocol development and data analyses.

10.1.11 Internal safety committee

Applicable only to the safety cohorts: An internal safety committee (ISC) will be established for the safety cohorts of this study to evaluate patients' safety. The ISC will be tasked with making decisions based on their review to continue, modify, or stop recruitment or the trial based on their assessment of the safety data. The membership, key responsibilities, and the corresponding procedures will be defined in the ISC Charter.

10.1.12 Independent data monitoring committee

Applicable only to the main cohort: An independent data monitoring committee (IDMC) will be established for the main cohort to safeguard the interest and safety of the patients participating in the study and provide independent review and assessment of the efficacy and safety data in a systematic manner.

The IDMC will be tasked with making a recommendation to the sponsor based on their review to continue, modify, or stop recruitment or the trial based on their assessment of efficacy and safety information. The membership, key responsibilities, and the corresponding procedures will be defined in the IDMC Charter.

10.1.13 Future research

Biological samples collected during this study may be stored for future research by the sponsor. Storage conditions will be in compliance with the standards for repositories of biological samples, according to the "Recommendation CM/Rec (2016)6 of the Committee of Ministers to member States on research on biological materials of human origin."[28]

The repository will have independent monitoring that will guarantee protection of the data and the patients' interests (also see section 10.1.4). Except for contractors of the sponsor, the samples will not be transferred to third parties, and they will not be sold to third parties. The exploratory studies that will be conducted with the samples will undergo a rigorous independent review evaluating both ethical and scientific aspects.

10.2 Appendix 2: Description of the iRECIST process for assessment of disease progression

iRECIST is based on RECIST 1.1 but adapted to account for the unique tumor response seen with immunotherapeutic drugs. iRECIST will be used by the investigator to assess tumor response and progression, and to guide decisions about changes in management.

10.2.1 Assessment at screening and prior to RECIST 1.1 progression

Until radiographic disease progression based on RECIST 1.1, there is no distinct iRECIST assessment.

10.2.2 Assessment and decision at RECIST 1.1 progression

Patients who show radiological disease progression by RECIST 1.1 will continue treatment until repeat scans are obtained, as described in section 8.1.2.

Tumor flare may manifest as any factor causing radiographic progression per RECIST 1.1, including:

- Increase in the sum of diameters of target lesion(s) identified at baseline to ≥20% and ≥5 mm from nadir

  Note: The iRECIST publication uses the terminology "sum of measurements", but "sum of diameters" will be used in this Protocol, consistent with the original RECIST 1.1 terminology.

- Unequivocal progression of non-target lesion(s) identified at baseline
- Development of new lesion(s)

iRECIST defines new response categories, including unconfirmed progressive disease (iUPD) and confirmed progressive disease (iCPD). For purposes of iRECIST assessment, the first visit showing progression according to RECIST 1.1 will be assigned a visit (overall) response of iUPD, regardless of which factors caused the progression.

At this visit, target and non-target lesions identified at baseline by RECIST 1.1 will be assessed as usual.

New lesions will be classified as measurable or non-measurable, using the same size thresholds and rules as for baseline lesion assessment in RECIST 1.1. From measurable new lesions, up to 5 lesions total (up to 2 per organ) may be selected as new lesions – target. The sum of

diameters of these lesions will be calculated and kept distinct from the sum of diameters for target lesions at baseline. All other new lesions will be followed qualitatively as new lesions – non-target.

10.2.3 Assessment at the confirmatory scans

On the confirmatory scans, the patient will be classified as progression confirmed (with an overall response of iCPD), or as showing persistent unconfirmed progression (with an overall response of iUPD), or as showing disease stability or response (iSD/iPR/iCR according to iRECIST).

10.2.4 Confirmation of progression

Progression is considered confirmed, and the overall response will be iCPD, if any of the following occurs:

- Any of the factors that were the basis for the initial iUPD to show worsening
  - For target lesions, worsening is a further increase in the sum of diameters of ≥5 mm, compared to any prior iUPD time point
  - For non-target lesions, worsening is any significant growth in lesions overall, compared to a prior iUPD time point; this does not have to meet the "unequivocal" standard of RECIST 1.1
  - For new lesions, worsening is any of these:
    - An increase in the new lesion sum of diameters by ≥5 mm from a prior iUPD time point
    - Visible growth of new non-target lesions
    - The appearance of additional new lesions
- Any new factor appears that would have triggered disease progression by RECIST 1.1

10.2.5 Persistent iUPD

Progression is considered not confirmed, and the overall response remains iUPD, if:

- none of the progression-confirming factors identified above occurs, and
- the target lesion sum of diameters (initial target lesions) remains above the initial disease progression threshold (by RECIST 1.1).

Additional scans for confirmation are to be scheduled 4 to 8 weeks from the scans on which iUPD is seen. This may correspond to the next visit in the original visit schedule. The assessment of the subsequent confirmation scan proceeds in an identical manner, with possible outcomes of iCPD, iUPD, and iSD/iPR/iCR.

10.2.6 Resolution of iUPD

Progression is considered not confirmed, and the overall response becomes iSD/iPR/iCR, if:

- none of the progression-confirming factors identified above occurs, and
- the target lesion sum of diameters (initial target lesions) is not above the initial disease progression threshold.

The response is classified as iSD or iPR (depending on the sum of diameters of the target lesions), or iCR if all lesions resolve.

In this case, the initial iUPD is considered to be pseudoprogression, and the level of suspicion for progression is "reset". This means that the next visit that shows radiographic progression, whenever it occurs, is again classified as iUPD by iRECIST, and the confirmation process is repeated before a response of iCPD can be assigned.

10.2.7 Management following the confirmatory scan

If repeat scans do not confirm disease progression per iRECIST, as assessed by the investigator, and the patient continues to be clinically stable, study interventions are to continue and the regular scan schedule is to be followed. If disease progression is confirmed, patients may be discontinued from study interventions.

Note: If a patient has iCPD and clinically meaningful, study interventions may be continued after consultation with the sponsor. In this case, if study interventions are continued, tumor imaging should continue to be performed following the intervals as outlined in section 8.1.

10.2.8 Detection of progression at visits after pseudoprogression resolves

After resolution of pseudoprogression (i.e., after iSD/iPR/iCR), another instance of progression (another iUPD) is indicated by any of the following events:

- Target lesions
  - Sum of diameters reaches the disease progression threshold (≥20% and ≥5 mm increase from nadir) either for the first time or after resolution of previous pseudoprogression. The nadir is always the smallest sum of diameters seen during the entire trial, either before or after an instance of pseudoprogression.
- Non-target lesions
  - If non-target lesions have never shown unequivocal progression, their doing so for the first time results in iUPD.
  - If non-target lesions have shown previous unequivocal progression, and this progression has not resolved, iUPD results from any significant further growth of non-target lesions, taken as a whole.
- New lesions
  - New lesions appear for the first time
  - Additional new lesions appear
  - Previously identified new target lesions show an increase of ≥5 mm in the new lesion sum of diameters, from the nadir value of that sum
  - Previously identified non-target lesions show any significant growth

If any of the events above occur, the overall response for that visit is iUPD, and the iUPD evaluation process (see section 10.2.3) is repeated. Progression must be confirmed before iCPD can occur.

The decision process on the subsequent iUPD is identical to the iUPD confirmation process for the initial disease progression, with one exception, which can occur if new lesions had occurred at a prior instance of iUPD, had not resolved, then worsened (increase in size or number)

leading to the second iUPD. If new lesion worsening has not resolved at the confirmatory scan, then iUPD cannot resolve to iSD or iPR. It will remain iUPD until either a decrease in the new lesion burden allows resolution to iSD or iPR, or until new or worsening causes of progression indicates iCPD.

Additional details about iRECIST are provided in the iRECIST publication.[20]

10.3 Appendix 3: Hy's law

Drugs are likely to cause a high rate (10-50%) of fatal liver injury or need for transplant in patients with acute hepatocellular injury sufficient to cause jaundice. Hy's law is a rule of thumb that a patient is at high risk of a fatal drug-induced liver injury if given a medication that causes hepatocellular injury (not cholestatic injury) with jaundice.

Hy's law cases have three components:

- The drug causes hepatocellular injury, generally defined as an elevated ALT or AST by 3-fold or greater above the ULN. Often with aminotransferases much greater (5-10×ULN).
- Among patients showing such aminotransferase elevations, they also have elevation of their serum total bilirubin of greater than 2×ULN, without findings of cholestasis (defined as serum alkaline phosphatase (ALP) activity less than 2×ULN).

No other reason can be found to explain the combination of increased aminotransferase and serum total bilirubin, such as viral hepatitis, alcohol abuse, ischemia, preexisting liver disease, or another drug capable of causing the observed injury.[29]

10.4 Appendix 4: Cockcroft-Gault formula

For males, creatinine clearance is estimated using the Cockcroft-Gault formula as follows:

Creatinine clearance = [(140 − age) × weight]/(72 × serum creatinine)

Where age is in years, weight is in kilograms, and serum creatinine is in mg/dL. Actual, not ideal weight is to be used.

For females, creatinine clearance is estimated by multiplying the result of the above formula by 0.85.

10.5 Appendix 3: Abbreviations

Abbreviation	Term
ADA	Anti-drug antibody
ADCC	Antibody-dependent cellular cytotoxicity
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ASaT	All-subjects-as-treated
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BOR	Best overall response (according to RECIST 1.1)
BRAF	V-raf murine sarcoma viral oncogene homolog B1
CA	Competent authority
CBR	Clinical benefit rate (according to RECIST 1.1)
CD	Cluster of differentiation
CFR	Code of federal regulations
CI	Confidence interval
CL	Apparent systemic clearance
C_{max}	Observed maximum serum concentration
CR	Complete response (according to RECIST 1.1)
CRA	Clinical research associate
CRO	Contract research organization
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor DNA
C_{trough}	Pre-dose concentration
DLT	Dose-limiting toxicity
DoR	Duration of response (according to RECIST 1.1)
EC	Ethics committee
ECG	Electrocardiography
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EEA	European Economic Area
EGFR	Epidermal growth factor receptor
Fc	Fragment crystallizable
FDA	US Food and Drug Administration
GCP	Good Clinical Practice

Abbreviation	Term
HBV	Hepatitis B
HCV	Hepatitis C
IB	Investigator's Brochure
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 (according to iRECIST)
iCR	Complete response (according to iRECIST)
IDMC	Independent Data Monitoring Committee
iDoR	Duration of response (according to iRECIST)
IEC	Independent ethics committee
Ig	Immunoglobulin
IL	Interleukin
ILD	Interstitial lung disease
iORR	Objective response rate (according to iRECIST)
iPFS	Progression-free survival (according to iRECIST)
iPR	Partial response (according to iRECIST)
IRB	Institutional review board
iRECIST	Response Evaluation Criteria In Solid Tumors for immune-based therapeutics
ISC	Internal safety committee
iSD	Stable disease (according to iRECIST)
iTtP	Time to progression (according to iRECIST)
iTtR	Time to response (according to iRECIST)
iUPD	Unconfirmed progressive disease (according to iRECIST)
K-RAS	Kirsten rat sarcoma viral oncogene homolog
MRI	Magnetic resonance imaging
NK	Natural killer
NKG2A	Inhibitory natural killer cell receptor
NKG2D	Activating natural killer cell receptor
NKp30	Natural killer protein 30; activating natural killer cell receptor
N-RAS	Neuroblastoma rat sarcoma viral oncogene homolog
ORR	Objective response rate (according to RECIST 1.1)
OS	Overall survival
PFS	Progression-free survival (according to RECIST 1.1)

Abbreviation	Term
PFS2	Progression-free survival on next-line anti-cancer treatment
PK	Pharmacokinetic(s)
PP	Per Protocol
PR	Partial response (according to RECIST 1.1)
Q1	25th percentile
Q3	75th percentile
R_{AUC}	Accumulation ratio
RAS	Rat sarcoma viral oncogene homolog
R_{Cmax}	Accumulation ratio
RECIST 1.1	Response Evaluation Criteria In Solid Tumors version 1.1
RP2D	Recommended phase 2 dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease (according to RECIST 1.1)
SmPC	Summary of Product Characteristics
$T_{1/2}$	Apparent terminal elimination half-life
TEAE	Treatment-emergent adverse event
T_{max}	Time to maximum serum concentration
TtP	Time to progression (according to RECIST 1.1)
TtR	Time to response (according to RECIST 1.1)
ULN	Upper limit of normal
V_{ss}	Apparent volume of distribution at steady state
V_z	Apparent volume of distribution during terminal phase
WOCBP	Woman of childbearing potential

Abbreviations of commonly used weight, height, and volume measures are not listed above.

10.6 Appendix 4: Protocol Amendment history

The PROTOCOL AMENDMENT SUMMARY OF CHANGES for the current amendment is located directly before the TABLE OF CONTENTS.

11 REFERENCES

1. Ritter CA, Arteaga CL. The epidermal growth factor receptor-tyrosine kinase: a promising therapeutic target in solid tumors. *Seminars in oncology.* 2003;30(1 Suppl 1):3-11.
2. Heinemann V, Stintzing S, Kirchner T, Boeck S, Jung A. Clinical relevance of EGFR- and KRAS-status in colorectal cancer patients treated with monoclonal antibodies directed against the EGFR. *Cancer Treat Rev.* 2009;35(3):262-271.
3. Ferris RL, Lenz HJ, Trotta AM, et al. Rationale for combination of therapeutic antibodies targeting tumor cells and immune checkpoint receptors: Harnessing innate and adaptive immunity through IgG1 isotype immune effector stimulation. *Cancer Treat Rev.* 2018;63:48-60.
4. Bessard A, Solé V, Bouchaud G, Quéméner A, Jacques Y. High antitumor activity of RLI, an interleukin-15 (IL-15)-IL-15 receptor alpha fusion protein, in metastatic melanoma and colorectal cancer. *Mol Cancer Ther.* 2009;8(9):2736-2745.
5. Antosova Z, Podzimkova N, Jiratova M, et al. 562 SO-C101 induces NK cell cytotoxicity and potentiates antibody-dependent cell cytotoxicity and anti-tumor activity. *J Immunother Cancer.* 2020;8(Suppl 3):A339-A339.
6. Palová L. 510 SO-C101, a high-affinity IL-15Rbg agonist, induces safe and potent anti-tumor immune activities in patients with solid tumors and supports further clinical investigations. 2021;9(Suppl 2):A541-A541.
7. Ferlay J, Ervik M, Colombet M, et al. Global Cancer Observatory: Cancer Today. https://gco.iarc.fr/today/home. Published 2020. Accessed February 28, 2022.
8. Li J, Ma X, Chakravarti D, Shalapour S, DePinho RA. Genetic and biological hallmarks of colorectal cancer. *Genes Dev.* 2021;35(11-12):787-820.
9. Sorich MJ, Wiese MD, Rowland A, Kichenadasse G, McKinnon RA, Karapetis CS. Extended RAS mutations and anti-EGFR monoclonal antibody survival benefit in metastatic colorectal cancer: a meta-analysis of randomized, controlled trials. *Ann Oncol.* 2015;26(1):13-21.
10. Misale S, Yaeger R, Hobor S, et al. Emergence of KRAS mutations and acquired resistance to anti-EGFR therapy in colorectal cancer. *Nature.* 2012;486(7404):532-536.
11. Van Cutsem E, Cervantes A, Adam R, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann Oncol.* 2016;27(8):1386-1422.
12. Benson AB, Venook AP, Al-Hawary MM, et al. Colon Cancer, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network : JNCCN.* 2021;19(3):329-359.
13. Harding J, Burtness B. Cetuximab: an epidermal growth factor receptor chemeric human-murine monoclonal antibody. *Drugs of today (Barcelona, Spain : 1998).* 2005;41(2):107-127.
14. Rocca YS, Roberti MP, Juliá EP, et al. Phenotypic and Functional Dysregulated Blood NK Cells in Colorectal Cancer Patients Can Be Activated by Cetuximab Plus IL-2 or IL-15. *Front Immunol.* 2016;7:413.

15. Ochoa MC, Minute L, López A, et al. Enhancement of antibody-dependent cellular cytotoxicity of cetuximab by a chimeric protein encompassing interleukin-15. *Oncoimmunology.* 2018;7(2):e1393597.
16. SOTIO data on file.
17. Erbitux USPI. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125084s279lbl.pdf. Accessed February 28, 2023.
18. Erbitux SmPC. https://www.ema.europa.eu/en/documents/product-information/erbitux-epar-product-information_en.pdf. Accessed February 28, 2023.
19. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *European journal of cancer (Oxford, England : 1990).* 2009;45(2):228-247.
20. Seymour L, Bogaerts J, Perrone A, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. *Lancet Oncol.* 2017;18(3):e143-e152.
21. Price TJ, Peeters M, Kim TW, et al. Panitumumab versus cetuximab in patients with chemotherapy-refractory wild-type KRAS exon 2 metastatic colorectal cancer (ASPECCT): a randomised, multicentre, open-label, non-inferiority phase 3 study. *Lancet Oncol.* 2014;15(6):569-579.
22. Lee DW, Santomasso BD, Locke FL, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. *Biology of Blood and Marrow Transplantation.* 2019;25(4):625-638.
23. Maus MV, Alexander S, Bishop MR, et al. Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune effector cell-related adverse events. *J Immunother Cancer.* 2020;8(2).
24. Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. *Blood.* 2014;124(2):188-195.
25. Meid AD, Bighelli I, Mächler S, et al. Combinations of QTc-prolonging drugs: towards disentangling pharmacokinetic and pharmacodynamic effects in their potentially additive nature. *Ther Adv Psychopharmacol.* 2017;7(12):251-264.
26. Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. *Biometrika.* 1934;26(4):404-413.
27. International Council for Harmonisation. E6 Good Clinical Practice Guideline. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4_2016_1109.pdf. Published 2016. Accessed February 28, 2023.
28. Council of Europe Committee of Ministers. Recommendation CM/Rec (2016)6 of the committee of ministers to member states on research on biological materials of human origin. https://search.coe.int/cm/Pages/result_details.aspx?ObjectId=090000168064e8ff. Published 2016. Accessed February 28, 2023.
29. U.S. Food and Drug Administration. Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation. https://www.fda.gov/media/116737/download. Published 2009. Accessed February 28, 2023.