STATISTICAL ANALYSIS PLAN

A Phase Ib/II open label study to assess the safety and pharmacokinetics of NUC-3373, a nucleotide analogue, given in combination with standard agents used in colorectal cancer treatment

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
C0D1	Cycle 0, day 1
C1D1	Cycle 1, day 1
CR	Complete response
CRC	Colorectal cancer
CRF	Case report forms
DCR	Disease control rate
DLT	Dose limiting toxicity
DoR	Duration of response
DoSD	Duration of stable disease
DSMC	Data safety monitoring committee
ECG	Electrocardiogram
EFR	Evaluable for response
FAS	Full analysis set
GCP	Good clinical practice
IV	Intravenously
Q1W	Weekly
Q2W	Fortnightly
LV	Leucovorin
NCI CTCAE	Common terminology criteria for adverse events published by the national cancer institute
NE	Not evaluable
NTL	Non-target lesions
ORR	Objective response rate
PD	Progressive disease
PDy	Pharmacodynamics
PFS	Progression-free survival
PK	Pharmacokinetics
PR	Partial response
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SOC	System organ classification
TEAE	Treatment emergent adverse event
TL	Target lesion
TS	Thymidylate synthase
TSz	Tumour size
ULN	Upper limit of normal
WHO	World health organization

1 INTRODUCTION

This document describes the statistical methods and data presentations to be used in the summary and analysis of safety, efficacy, and pharmacokinetic data from Protocol NuTide:302. Background information is provided for the overall study design and objectives. The reader is referred to the study protocol and electronic case report forms (eCRFs) for details of study conduct and data collection.

1.1 STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE

The following changes were made compared to the first version of the SAP:

Version	Date	Change number	Change description
2	04-OCT-2019	1	Study Objectives, treatments and endpoints are updated by adding third arm.
		2	Secondary Objectives are updated
		3	Exploratory Objectives are updated
		4	Overall study design is updated
3	04-FEB-2022	1	Exploratory Objectives are updated
		2	Overall study design is updated
		3	Baseline definition is updated
		4	Overall Survival is included
4	17-AUG-2023	1	FAS Population is updated
		2	Baseline definition is updated for clarification
		3	Change from baseline in tumor size explanation for clarification is added
		4	Duration of stable disease is clarified
		5	Laboratory evaluation is clarified

2 STUDY OBJECTIVES, TREATMENTS, AND ENDPOINTS

This study consists of two phases (Phase Ib and Phase II) and includes three study parts (Parts 1, 2 and 3) with several treatment arms within each part. Phase Ib includes Part 1 (Arms 1a-1d) and Part 2 (Arms 2a-2d) and Phase II includes Part 3 (Arms 3a-3g).

In Part 1, initially ≥3rd-line patients will be randomised to receive a single dose of NUC-3373, followed by a 2-week washout, and then receive NUC-3373 in combination with leucovorin (LV) every two weeks, or to receive an initial dose of NUC-3373 in combination with LV, followed by a 2-week washout, and then receive NUC-3373 without LV every two weeks. Upon completion of these administration arms, a third arm will be enrolled to receive NUC-3373 in combination with LV every week. A fourth arm will be included to further assess the safety and tolerability of NUC-3373 with LV every week in patients who are ineligible for combination chemotherapy.

In Part 2, patients will be enrolled in parallel cohorts of NUC-3373 + LV weekly (Q1W), in combination with either fortnightly (Q2W) oxaliplatin (NUFOX) or Q2W irinotecan (NUFIRI), with a dose escalation of NUC-3373. Once the escalation groups have been completed, an expansion part with the recommended dose determined from this initial part will be performed with the same combinations to further assess the safety, tolerability and preliminary efficacy of these NUFOX and NUFIRI regimens (Q1W NUC-3373 + LV; Q2W oxaliplatin or irinotecan).

In Part 3, patients will be enrolled in parallel cohorts of Q1W NUFOX and NUFIRI regimens administered in combination with bevacizumab (Q2W arms may also be opened). NUFOX and NUFIRI regimens may also be administered in combination with cetuximab or panitumumab, depending on emerging data. In addition, Q1W NUC-3373 + LV in combination with bevacizumab may be assessed in patients qualifying for maintenance therapy.

2.1 STUDY OBJECTIVES

2.1.1 Primary Objective

Phase Ib

The primary objective is to identify a recommended dose and schedule for NUC-3373 when combined with other agents commonly used in treatment of advanced colorectal cancer (CRC), including:

- LV
- oxaliplatin
- oxaliplatin and vascular endothelial growth factor (VEGF) pathway inhibitors (bevacizumab)

- oxaliplatin and epidermal growth factor receptor (EGFR) inhibitors (cetuximab or panitumumab)
- irinotecan
- irinotecan and VEGF pathway inhibitors (bevacizumab)
- irinotecan and EGFR inhibitors (cetuximab or panitumumab)

Phase II

To explore the anti-cancer activity of NUC-3373 when combined with other agents commonly used in the treatment of advanced CRC using Response Evaluation in Solid Tumours (RECIST) v1.1 criteria.

2.1.2 Secondary Objectives

Secondary objectives of this study are:

- To assess the safety and tolerability of each NUC-3373 containing regimen (Phase Ib and Phase II)
- To assess the pharmacokinetics (PK) of NUC-3373, oxaliplatin, irinotecan and their metabolites in each NUC-3373 containing regimen. (Phase Ib and Phase II, not in the scope of this statistical analysis plan [SAP]).
- To make a preliminary assessment of the anti-tumour activity of NUC-3373 alone and in each NUC-3373 containing regimen (Phase Ib only).
- To conduct a within-patient and a between-patient analysis of the effect of LV when added to NUC-3373 on intracellular pharmacodynamic (PDy) parameters and haematological parameters and use this information to determine if the addition of LV to NUC-3373 containing regimens is required for clinical activity (Part 1 Arm 1a and Arm 1b only).

2.1.3 Exploratory Objectives

Exploratory objectives of this study are:

- To explore predictive biomarkers of biological activity and possible relationships between PK and PDy effects (Phase Ib and Phase II).
- Depending on emerging data, to potentially conduct a within-patient analysis of the effect of combining NUC-3373 with irinotecan on the plasma PK parameters of both NUC-3373 and irinotecan. (Not in the scope of this statistical analysis plan [SAP]; Part 2 Arm 2b sub-study only).

2.2 TREATMENT GROUPS

The treatment groups in the study are as follows:

Phase Ib

Part 1 (≥3rd-line and combination chemotherapy ineligible patients)

Part 1 determined that NUC-3373 should be administered with LV (Arms 1a, 1b and 1c) and will further assess the safety and tolerability of NUC-3373 + LV on a Q1W schedule (Arm 1d).

Arm 1a (≥3rd-line patients): NUC-3373 administered intravenously (IV) at 1500 mg/m^2 over 120 minutes followed by a 14-day washout period. Thereafter, on Day 1 and 15 of 28-day cycle, LV was administered by IV infusion at 400 mg/m^2 over 120 minutes followed by NUC-3373 administration by IV infusion at the cohort-prescribed dose level.

Arm 1b (≥3rd-line patients): LV was administered at 400 mg/m^2 by IV infusion over 120 minutes, followed by NUC-3373 infusion at 1500 mg/m^2 over 120 minutes. LV was not administered again in Arm 1b. After a 14-day washout period, NUC-3373 was administered on Days 1 and 15 of 28-day cycles by IV infusion at the cohort prescribed dose level.

Arm 1c (≥3rd-line patients): On Days 1, 8, 15 and 22 of 28-day cycles, LV was administered by IV infusion at 400 mg/m^2 over 120 minutes, followed by NUC-3373 administration by IV infusion at the cohort-prescribed dose level.

Arm 1d (combination chemotherapy ineligible patients): On Days 1, 8, 15 and 22 of 28-day cycles, LV will be administered by IV infusion at 400 mg/m^2 over 120 minutes, followed by NUC-3373 administration by IV infusion at 2500 mg/m^2 over 200 minutes.

Data from Arms 1a and 1b of the study showed that LV did not impact the safety or PK of NUC-3373; therefore, the decision was made that LV should be administered at 400 mg/m^2 on each day of NUC-3373 administration in all parts of the study.

Part 2 Dose Escalation (≥3rd-line patients)

Part 2 will assess the safety and tolerability of different doses of Q1W NUC-3373 + LV when administered in combination with either oxaliplatin (NUFOX) or irinotecan (NUFIRI).

Arm 2a: NUC-3373 + LV will be administered Q1W and oxaliplatin (85 mg/m^2) will be administered Q2W in 28-day cycles.

Arm 2b: NUC-3373 + LV will be administered Q1W and irinotecan (180 mg/m^2) will be administered Q2W in 28-day cycles.

Arm 2c: NUC-3373 + LV will be administered Q1W and oxaliplatin (85 mg/m^2) will be administered Q2W in 28-day cycles.

Arm 2d: NUC-3373 + LV will be administered Q1W and irinotecan (180 mg/m^2) will be administered Q2W in 28-day cycles.

Following determination of the recommended doses within the NUFOX and NUFIRI regimens in the Part 2 dose escalation phase, Part 3 will open in parallel to the Part 2 expansion phase.

Phase II

Part 3 (2nd-line patients and maintenance patients)

Part 3 will assess the safety and efficacy of Q1W NUFOX and NUFIRI regimens administered in combination with bevacizumab (Q2W arms may also be opened). NUFOX and NUFIRI regimens may also be administered in combination with cetuximab or panitumumab, depending on emerging data. In addition, Q1W NUC-3373 + LV in combination with bevacizumab may be assessed in patients qualifying for maintenance therapy.

Arm 3a (2nd-line patients): NUC-3373, LV and oxaliplatin at dose levels used in Arm 2a will be combined with bevacizumab. NUC 3373 and LV will be administered Q1W and oxaliplatin and bevacizumab will be administered Q2W.

Arm 3b (2nd-line patients)**:** NUC-3373, LV and oxaliplatin at dose levels used in Arm 2a will be combined with bevacizumab. NUC-3373, LV, oxaliplatin and bevacizumab will be administered Q2W.

Arm 3c (2nd-line patients): NUC-3373, LV and irinotecan at dose levels used in Arm 2b will be combined with bevacizumab. NUC-3373 and LV will be administered Q1W and irinotecan and bevacizumab will be administered Q2W.

Arm 3d (2nd-line patients): NUC-3373, LV and irinotecan at dose levels used in Arm 2b will be combined with bevacizumab. NUC-3373, LV, irinotecan and bevacizumab will be administered Q2W.

Arm 3e (Maintenance patients): NUC-3373 (2500 mg/m^2 Q1W) + LV (400 mg/m^2 Q1W) will be combined with bevacizumab (5 mg/kg Q2W).

Arm 3f (2nd-line patients): NUC-3373, LV and oxaliplatin at dose levels used in Arm 2a may be administered in subsequent cetuximab cohorts. NUC-3373 + LV may be administered Q1W or Q2W, oxaliplatin will be administered Q2W and cetuximab will be administered Q1W.

Arm 3g (2nd-line patients): NUC-3373, LV and irinotecan at dose levels used in Arm 2b may be administered in subsequent cetuximab cohorts. NUC-3373 + LV may be administered Q1W or Q2W, irinotecan will be administered Q2W and cetuximab will be administered Q1W.

Different patient populations will be included in the study as follows:

- Part 1 (Part 1a, 1b and 1c) all are ≥3rd line patients
- Part 2 (Part 2a, 2b, and 2b sub-study) all are ≥3rd line patients
- Part 3 (Part 3a, 3c) all are 2nd line patients

If positive efficacy signals are observed in any of the patient populations included in Parts 1, 2 or 3 of the study, expansion cohorts may be opened to further assess efficacy in approximately 20 patients per cohort.

A Q2W schedule may be explored at any time, depending on emergent safety, efficacy and PK data.

2.3 STUDY ENDPOINTS

Endpoints are applicable for all parts unless otherwise stated.

2.3.1 Primary Endpoint

Phase Ib
To identify a recommended dose and schedule for NUC-3373 when combined with LV and other agents routinely used in the treatment of patients with advanced CRC.

Phase II
Objective disease assessment by radiographic imaging will be performed every 8 weeks and analysed using RECIST v1.1 criteria. Anti-tumour activity will be assessed on the basis of:

- Percentage change from baseline in tumour size
- Objective Response Rate (ORR)
- Disease Control Rate (DCR)
- Duration of Response (DoR)
- Duration of Stable Disease (DoSD)
- Progression-Free Survival (PFS)
- Overall Survival (OS) rate at 6 and 12 months

2.3.2 Secondary Endpoints

Safety endpoints (Phase Ib and Phase II):

- Treatment emergent adverse events (TEAEs) throughout the study (as per the Common Terminology Criteria for Adverse Events published by the National Cancer Institute [NCI CTCAE] Version 5.0)
- Clinically significant laboratory changes (as per the NCI CTCAE Version 5.0) throughout the study
- Changes in physical examination, vital signs and serial electrocardiograms (ECGs) throughout the study

Endpoints for the PK are not within the scope of this SAP.

Efficacy endpoints are (Phase Ib):
Objective disease assessment by radiographic imaging will be performed every 8 weeks and analysed using RECIST version 1.1. Anti-tumour activity will be assessed on the basis of:

- Percentage change from baseline in tumour size

- ORR
- DCR
- DoR
- DoSD
- PFS
- OS rate at 6 and 12 months

2.3.3 Exploratory Endpoints (Phase Ib and Phase II)

- Pre-treatment and on-treatment measurements of PDy markers in peripheral blood mononuclear cells (PBMCs) (Part 1 only)
- Exploration of predictive biomarkers such as gene expression and/or genetic alterations in blood and tumour (*e.g.* genetic alterations in genes involved in PK exposure, PDy effects, safety and efficacy)
- DNA/RNA and protein analysis of pre- and on-treatment tumour samples.

Exploratory endpoints for PK are not within the scope of this SAP.

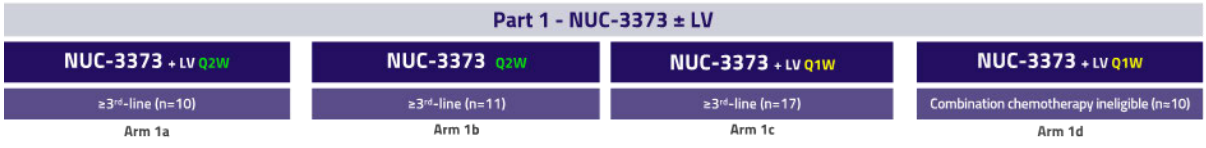
3 STUDY DESIGN

3.1 OVERALL STUDY DESIGN

This is a three-part, Phase Ib/II study of NUC-3373 administered by IV infusion (Q1W or Q2W), either as monotherapy or as part of various combinations with LV, oxaliplatin, irinotecan, VEGF inhibitors and EGFR inhibitors. Phase Ib includes Part 1 (Arms 1a-1d) and Part 2 (Arms 2a-2d) and Phase II includes Part 3 (Arms 3a-3g). The opening and timing of study arms will depend on emerging data.

It is anticipated that approximately 215 patients with advanced or metastatic radiologically measurable CRC may be required in this study. Additional patients may be enrolled in all parts of the study to replace patients who withdraw prior to completing Cycle 0 (where relevant) and the initial 28-day safety evaluation in Cycle 1. Additionally, if the Data Safety Monitoring Committee (DSMC) determine that an increased number of patients are required to evaluate alternate doses within a study part, enrolment in a cohort may be expanded. If positive efficacy signals are observed in any of the patient populations included in Parts 1, 2 or 3 of the study, expansion cohorts may be opened to further assess safety and efficacy in approximately 20 patients per cohort.

3.1.1 Part 1



Part 1 determined that NUC-3373 should be administered with LV (Arms 1a, 1b and 1c) and will further assess the safety and tolerability of NUC-3373 + LV (Arm 1d) in patients with advanced or metastatic CRC. Initially, ≥3rd-line patients will be randomised via block randomisation to two parallel arms, each receiving NUC-3373Q2W either with LV (Arm 1a) or without LV (Arm 1b). Upon completion of the Q2W dose administration arms, a third arm of up to 12 evaluable ≥3rd-line patients will be enrolled to a Q1W administration schedule of NUC-3373 + LV (Arm 1c). Arms 1a, 1b, and 1c are now complete. Following this, approximately 10 combination chemotherapy ineligible patients will be enrolled to a Q1W administration schedule of NUC-3373 plus LV (Arm 1d).

In Arm 1a, an initial arm of up to 6 evaluable patients will receive a single dose of NUC-3373, at 1500 mg/m^2. This visit will be considered Cycle 0, Day 1 (C0D1) for the purposes of the study visits. The initial dose will be followed by a 2-week washout period, during which safety and PK/PDy will be monitored. The next dose of NUC-3373 will be given in combination with LV at 400 mg/m^2. This visit will be considered Cycle 1, Day 1 (C1D1) for the purposes of the study visits. All subsequent doses of NUC-3373 will be given Q2W in combination with LV in 28-day cycles. A total of 10 patients were finally enrolled in Arm 1a to obtain 6 evaluable patients.

In Arm 1b, an initial arm of up to 6 evaluable patients will receive a single dose of NUC-3373 at 1500 mg/m^2 in combination with LV at 400 mg/m^2. This visit will be considered C0D1 for the purposes of the study visits. The initial combination dose will be followed by a 2-week washout period during which safety and PK/PDy will be monitored. The next dose of NUC-3373 will be given without LV. This visit will be considered C1D1 for the purposes of the study visits. All subsequent doses of NUC-3373 will be given Q2W without LV in 28-day cycles. A total of 11 patients were finally enrolled in Arm 1b to obtain 6 evaluable patients.

In Arm 1c, two initial cohorts of up to 12 evaluable patients each will receive NUC-3373 Q1W at either 1500 mg/m^2 or 2500 mg/m^2 in combination with LV Q1W at 400 mg/m^2. NUC-3373 and LV will be administered on Days 1, 8, 15 and 22 of 28-day cycles. A total of 17 patients were finally enrolled in Arm 1c to obtain 6 evaluable patients per cohort.

In Arm 1d, a cohort of approximately 10 combination chemotherapy ineligible patients will receive NUC-3373 at 2500 mg/m^2 in combination with LV at 400 mg/m^2. NUC-3373 + LV will be administered on Days 1, 8, 15 and 22 of 28-day cycles.

All patients in Part 1 (Arms 1a, 1b, 1c) will be monitored for dose-limiting toxicities (DLTs) up to Day 28 of Cycle 1.

If the dose of NUC-3373 is not tolerable or is sub-optimal, alternate dose levels may be explored. If cohorts at additional doses are opened, these will utilise a modified 3+3 design in which a fourth patient may be added to each initial 3-patient cohort to account for a patient that may become unevaluable for DLT evaluation for any reason other than safety. There will be a 7-day observation period between treatment of the first patient and treatment of subsequent patients in a cohort.

Once a minimum of 3 patients in each of Arms 1a, 1b and 1c have completed the 28-day DLT evaluation period all available safety data, PK and PDy data will be evaluated to establish the tolerability of NUC-3373±LV administered in each dose administration schedule.

Patients who completed the DLT period may be switched from a Q1W to a Q2W schedule if they experienced drug-related toxicity (other than fatigue) that would otherwise have led to treatment discontinuation. In addition, patients who completed the DLT period may be moved from a Q2W to a Q1W schedule. The decision to switch schedules will be discussed with and approved by the Sponsor on an individual patient basis.

In addition to the assessment of safety, tolerability, PK and PDy, a radiologic assessment of disease will be performed at 8-week intervals and evaluated using RECIST v1.1 to gain a preliminary assessment of clinical activity.

3.1.2 Part 2

Findings from Part 1 of the study showed that LV did not impact the safety or PK of NUC-3373; therefore, the decision was made that LV should be administered at 400 mg/m^2 on each day of NUC-3373 administration in all subsequent parts of the study.

Part 2 of the study consists of a dose escalation phase using a modified 3 + 3 design which may be followed by an expansion phase. The dose escalation phase will assess the safety and tolerability of different doses of NUC-3373 + LV when administered in combination with either oxaliplatin (NUFOX) or irinotecan (NUFIRI) in a Q1W schedule in ≥3rd-line patients. Oxaliplatin and irinotecan will be given at standard doses and schedules. In the expansion phase, cohorts of 2nd-/3rd-line patients may be enrolled to assess Q1W schedules of the NUFOX and NUFIRI regimens selected in the dose escalation phase.

The dose escalation group of patients will receive NUC-3373 + LV to assess the safety and tolerability of different doses of NUC-3373 + LV administered in combination with oxaliplatin (Arm 2a) or irinotecan (Arm 2b).

In Arm 2a, ≥3rd-line patients will receive NUC-3373 + LV on Days 1, 8, 15 and 22 and oxaliplatin on Days 1 and 15 of 28-day cycles.

In Arm 2b, ≥3rd-line patients will receive NUC-3373 + LV on Days 1, 8, 15 and 22 and irinotecan on Days 1 and 15 of 28-day cycles.

The starting dose of NUC-3373 will be 1500 mg/m^2 followed by dose escalation. Based on a clinical study of NUC-3373 (NuTide:301, EudraCT 2015-002250-13, NCT Number NCT02723240), alternate and/or additional dose levels may be considered and implemented upon recommendation of the DSMC.

The decision on which arm to enrol a patient to, Arm 2a or Arm 2b, will be made by the treating physician and will take into account the patient's clinical condition and prior therapies administered for treatment of CRC.

Patients will be enrolled into cohorts following a modified 3+3 design, in which a fourth patient may be enrolled in each initial 3-patient cohort as described above. The initial patient in each cohort will complete a 7-day observation period before subsequent patients are enrolled. All patients in Arm 2a and 2b will be monitored for DLTs up to day 28 of Cycle 1. Dose escalation or de-escalation decisions will be based on DSMC review once three patients have completed the first 28-day cycle.

The recommended dose of NUC-3373 + LV in combination with oxaliplatin (Arm 2a) or irinotecan (Arm 2b) will be determined separately, and may be different.

Patients who have completed the DLT period may be switched from a Q1W to a Q2W schedule if they experience drug-related toxicity (other than fatigue) that would otherwise lead to treatment discontinuation. In addition, patients who have completed the DLT period may move from a Q2W to a Q1W schedule. The decision to switch schedules must be discussed with and approved by the Sponsor on an individual patient basis.

Once the dose escalation groups have been completed, the DSMC will review the available safety, clinical activity and PK data to determine the recommended dose of NUC-3373 + LV when given in combination with oxaliplatin (NUFOX) or irinotecan (NUFIRI). If safety concerns arise, additional cohorts assessing alternative doses of oxaliplatin and irinotecan may be opened with agreement from the DSMC.

The MTD for NUFIRI has been established in Arm 2b and was determined to be 1500 mg/m^2 NUC-3373 + 400 mg/m^2 LV + 180 mg/m^2 irinotecan.

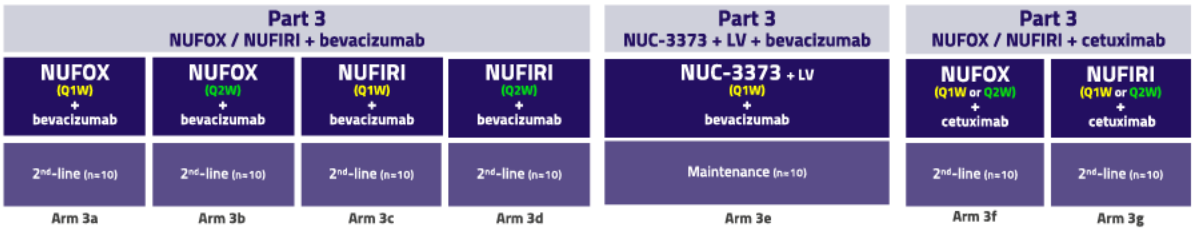
Expansion cohorts may be enrolled to Part 2 to further assess the safety, tolerability and preliminary efficacy of the Q1W NUFOX (Arm 2c) and NUFIRI (Arm 2d) regimens, using the dose of NUC-3373 selected in the dose escalation phase.

A PK sub-study may be conducted during Part 2 if emerging data suggest it would be beneficial to evaluate the PK relationship between NUC-3373, LV and irinotecan. If conducted, an additional 8 patients would be enrolled in the NUFIRI Q1W cohort (Arm 2b). Inclusion into this sub-study will also involve individual patient genotyping for drug metabolising enzymes and drug transporters to predict irinotecan-related toxicities. Genotyping will be performed for each patient using genomic DNA from white blood cells isolated from whole blood samples taken during screening. The genomic DNA will be analysed using pharmacogenomic protocols specific for individual genotypes for drug metabolising enzymes and drug transporters, e.g., TATA box polymorphism of the UGT1A1 promoter region and NR1I2-rs10934498

polymorphism, prior to admission to this sub-study. Genotyping is not required for patients who have a known UGT1A1 status from prior testing. In Cycle 1 of the sub study, irinotecan and LV will be administered concurrently on Day 1. On Day 8, NUC-3373 and LV will be administered sequentially. On Day 15, 4 patients (Group A) will first be administered irinotecan concurrently with LV, followed by NUC-3373. The remaining 4 patients (Group B) will first be administered NUC-3373, followed by irinotecan concurrently with LV. On Day 22, NUC-3373 and LV will be administered sequentially. On Cycle 2 Day 1 (29 days after the start of treatment), the infusion sequence will be reversed in a cross-over fashion whereby patients in Group A will first be administered NUC-3373, followed by irinotecan concurrently with LV and patients in Group B will first be administered irinotecan concurrently with LV, followed by NUC-3373. Patients will be alternately assigned to Group A or Group B. The doses of NUC-3373 and irinotecan used in the sub-study will be the recommended doses determined in Arm 2b.

Blood samples will be collected for PK analysis on Cycle 1 Day 1, Cycle 1 Day 8, Cycle 1 Day 15, Cycle 1 Day 22 and Cycle 2 Day 1. In addition, Holter ECG assessments will be performed on Cycle 1 Day 8 and Cycle 1 Day 22 during infusion and up to 24 hours post-infusion. Patients enrolled in the PK sub-study will be considered evaluable for PK endpoints if they have received planned study treatment and had PK assessments up to at least C1D15. If patients discontinue study treatment or require dose modifications before C1D15, they will be considered non-evaluable and will be replaced. Following this, patients will continue on the treatment schedule outlined for Arm 2b.

3.1.3 Part 3



In Part 3, Q1W NUFOX + bevacizumab and Q1W NUFIRI + bevacizumab cohorts (Arms 3a and 3c) will be opened first; the other arms may subsequently be opened, depending on emerging data

Following determination of the recommended NUFOX and NUFIRI regimens in the Part 2 dose escalation phase, Part 3 will open. The Part 2 expansion phase may open in parallel.

In Part 3, 2nd-line patients will receive the NUFOX and NUFIRI regimens selected in Part 2 in combination with bevacizumab. Q1W bevacizumab-containing arms will be opened first. Following this, Q2W arms and/or cetuximab combination arms may be opened, depending on emerging data. In addition, patients qualifying for maintenance therapy may receive NUC-3373 + LV in combination with bevacizumab.

The choice of arm to which an eligible patient should be enrolled will be at the Investigator's discretion, taking into account the patient's clinical condition and therapies that have previously been administered.

Bevacizumab and cetuximab should be used in accordance with standard local practice.

4 SAMPLE SIZE CONSIDERATIONS

The study is not formally powered, but has been designed to estimate the safety and tolerability of NUC-3373 when given with the combination agents described above. For the dose escalation phases, a modified 3+3 design has been selected to enable an assessment of safety and tolerability, whilst limiting the number of patients exposed to experimental treatment and procedures.

The following parts will recruit the following numbers of patients:

Part 1: Up to 50 patients
Part 2: Up to 65 patients
Part 3: Up to 100 patients

Total: Up to 215 patients.

5 ANALYSIS POPULATIONS

The following population definitions will be used in study summaries and analyses.

5.1 SAFETY

For each part of the study, the Safety Population includes all patients in that part of the study who have received at least one dose of NUC-3373 and will be the primary analysis set for the assessment of safety and tolerability in the study.

For the purpose of data summaries, patients will be included in the Safety Population according to the treatment cohort and dose level initially received, regardless of any subsequent dose adjustments.

5.2 FULL ANALYSIS SET

For all study parts and cohorts, the Full Analysis Set (FAS) is based on the intention-to-treat principles and includes all randomized patients . Patients will be analysed based on randomised treatment.

The FAS will be used to assess the PDy markers.

5.3 PER-PROTOCOL SET

Not applicable.

5.4 EVALUABLE FOR RESPONSE SET

The Evaluable for Response (EFR) set is defined as a subset of the FAS with measurable disease at baseline, and who have undergone at least two cycles of treatment, received at least 75% of planned treatment (all the treatments, entire regimen) over the two cycles, and undergone a post-treatment objective disease assessment. Patients will be included in the EFR based on the dose of NUC-3373 initially received, regardless of any subsequent dose adjustments.

The EFR set will be the primary analysis set used to assess tumour size, ORR, DCR, DoR and DoSD in all study parts.

5.5 PHARMACOKINETIC ANALYSIS SET

The PK Population is outside the scope of this analysis plan.

6 CONSIDERATIONS FOR DATA ANALYSIS

6.1 PROGRAMMING ENVIRONMENT

All analyses will be conducted using SAS® version 9.3 or higher.

6.2 STRATA AND COVARIATES

Not applicable.

6.3 SUBGROUPS

As deemed warranted by the data, efficacy may also be assessed in sub populations, as defined by the sponsor and documented in an update to this analysis plan prior to database lock. Sub-group analyses will assess consistency of treatment effect across potential or expected prognostic factors, or biomarkers. Analyses will not be performed if there are too few events available for a meaningful analysis of a particular sub-group.

6.4 MULTIPLE COMPARISONS AND MULTIPLICITY

There are no planned adjustments for multiplicity.

6.5 SIGNIFICANCE LEVEL

Unless otherwise noted, all statistical analyses will be conducted with significance level (α) of 0.05 and utilize two-sided testing.

6.6 STATISTICAL NOTATION AND METHODOLOGY

Unless stated otherwise, the term "descriptive statistics" refers to the number of patients, mean, median, standard deviation, interquartile range (for overall, for safety data only), minimum, and maximum for continuous data and frequencies and percentages for categorical data. Minimum and maximum values will be rounded to the precision of the original value, means and medians will be rounded to 1 decimal place greater than the precision of the original value, and standard deviations will be rounded to 2 decimal places greater than the precision of the original value. Percentages will be rounded to the nearest whole number (zeros are not displayed) with values of "< 1%" and "> 99%" shown as necessary for values falling near the boundaries. P-values will be presented with 3 decimal places and values less than 0.001 will be presented as < 0.001.

Unless otherwise noted, all data collected during the study will be included in data listings and will be sorted by cohort, patient number and then by date/time for each patient number.

All data from each study part will be presented separately in the tables, figures and listings. Furthermore, for Parts 2 and 3, data for each cohort will be presented separately.

Outputs will be provided for:

- DSMC for Arms 1a-c
- DSMC for Arm 1d

- DSMC for each of the 4 Part 2 cohorts (may be more than one DSMC)
- DSMC for each of the 6 Part 3 cohorts (may be more than one DSMC
- Final outputs for Part 1
- Final outputs for Part 2
- Final outputs for Part 3
- Final outputs for all 3 parts combined

For the final analysis, all data will be reported by cohort.

7 DATA HANDLING METHODS

7.1 VISIT WINDOWS

Study visit periods will be windowed as applicable according to the following:

- Screening: Days -28 to -1
- Baseline: Day 1, the last non-missing value prior to dosing with any part of the treatment regimen , regardless of the screening visit window. If at Day 1 the time is missing, we will consider all assessments which were required as 'pre-treatment' according to the protocol as baseline.
- On-Treatment: Treatment duration
- Post-Treatment: From last dose until disease progression, new treatment initiation, or death

Values will be presented for all scheduled study visits according to the nominal visit obtained from the CRF. If an unscheduled visit falls in a visit window with an existing nominal visit assessment, the nominal assessment will be used for summary presentation. If no nominal visit assessment exists for a visit window with unscheduled visit(s), then the latest unscheduled visit within the visit window will be used. If multiple nominal assessments are collected within the same visit, the latest value and corresponding date will be used for summary presentation.

For tumor assessments and lesions < 28 days prior to treatment will be taken into account.All values will be included in the data listings.

7.2 DATA DERIVATIONS AND DEFINITIONS

Baseline will be the last non-missing value prior to dosing with any part of the treatment regimen, regardless of the screening visit window. If at Day 1 the time is missing, we will consider all assessments which were required as 'pre-treatment' according to the protocol as baseline.

Study days on or after the initial dose of study drug will be computed as Study Day = Date – Study Drug Start Date + 1. For pre-dosing dates, Study Day = Date – Study Drug Start Date.

Treatment-emergent events will be considered as any event occurring after the first dose of study drug and up to 30 days after the last dose of study treatment.

When converting study days to months, the number of days in a month will be assumed to be 365.25/12.

The following will define prior medication use versus concomitant medication use:

- A prior medication is defined as any medication taken prior to the initiation of investigational drug irrespective of whether it is continued into the study.

- A concomitant medication is defined as any medication taken after the initiation of investigational drug and up to 30 calendar days after the last administration of investigational drug.

If a medication falls into both prior and concomitant time phase then it will be presented in both time phases.

7.3 MISSING DATA

7.3.1 Date Values

In cases of incomplete dates (*e.g.,* pertaining to adverse events [AE], concomitant medication, medical history, *etc.*), the missing component(s) will be assumed as the most conservative value(s) possible. For example, if the start date has a missing day value, the first day of the month will be imputed for study day computations (*i.e.,* treatment-emergent status, *etc*.) unless this proves to be off-treatment, in which case the date of initial dose of study drug will be used. If day is missing for an end date, the last day of the month will be imputed. Similar logic will be assumed for missing month and year components.

Date imputation will only be used for computational purposes e.g., treatment-emergent status, etc. Actual data values as they appear in the original CRFs will be shown in the data listings.

7.3.2 Non-Date Values

Every effort will be made to obtain the protocol-required data for all study assessments that are scheduled for each scheduled visit for all patients who have been enrolled.

In general, missing data will remain missing and will not be included in data summaries. Exceptions are described below.

Missing baseline data (safety data)
If a baseline value is not available and a screening value is available for the same endpoint, then the last screening value will be used as baseline. This value will also be used for calculations of changes from baseline. Baseline will be the last non-missing value prior to dosing with any part of the treatment regimen, regardless of the screening visit window. If at Day 1 the time is missing, we will consider all assessments which were required as 'pre-treatment' according to the protocol as baseline.

8 STUDY POPULATION

Unless otherwise stated, all study population analyses will be performed on the Safety Population (see section 5.1).

8.1 PATIENT DISPOSITION

Patient disposition will be presented for all patients.

The disposition of patients will be summarised presenting the number of patients enrolled, the number of patients treated, the number of patients who discontinued participation in the study by reason, and the number of patients who discontinued each study treatment by reason, by dose cohort and overall.

The number and percentage of patients included in each analysis population will be presented by dose cohort and overall.

8.2 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline disease characteristic data will be presented based on the FAS.

Baseline demographic and background data, including, but not limited to age, gender, weight, height, race, ethnicity and ECOG status will be listed and summarised using appropriate descriptive statistics by dose cohort and overall.

Baseline disease characteristics including, but not limited to primary diagnosis, primary tumour location and disease status at baseline will also be listed and summarised using appropriate descriptive statistics by dose cohort and overall.

8.3 PRIOR AND CONCOMITANT MEDICATIONS

Concomitant medications will be coded with the World Health Organization Drug Dictionary (WHO DD). Concomitant medications of specific interest will be defined prior to database lock and will be summarised with descriptive statistics by drug Anatomical Therapeutic Chemical (ATC) Classification System (level one), and generic name, by dose cohort and overall.

Prior medications will be listed only.

8.4 MEDICAL HISTORY

Medical history will be summarised with descriptive statistics for medical history code by dose cohort and overall.

The number of prior cancer regimens taken by each patient will be summarised, along with the mean number of prior cancer regimens and the number of patients with each type of cancer therapy (chemotherapy, biological therapy, immunotherapy, or other), by dose cohort and overall.

The number of prior radiation therapies taken by each patient will be summarised, along with the mean number of prior radiation therapies, by dose cohort and overall.

The number of prior cancer surgeries for each patient will be summarised, along with the mean number of prior cancer surgeries and the number of patients with each type of cancer surgery (diagnostic, therapeutic, or other), by dose cohort and overall.

Comprehensive data listings will also be included, including those of RAS status, archival tumour sample data and tumour biopsy sample data.

8.5 INCLUSION/EXCLUSION CRITERIA

Inclusion and exclusion criteria failures will be included in a data listing.

8.6 PROTOCOL DEVIATIONS

Deviations from the protocol will be summarised by category with descriptive statistics, by dose cohort and overall.

The following categories, which may impact on the efficacy, will be considered as major protocol deviations:

- Failure to meet inclusion criteria
- Meeting exclusion criteria
- Baseline RECIST out of 28-day window
- Non-compliance with study drug
- Taking prohibited concomitant medication

The following categories, which may impact on the efficacy, will be considered as minor protocol deviations:

- Issues with informed consent
- Visit out of window
- Evaluation or procedure required by protocol not completed
- Developing withdrawal criteria but not withdrawn
- Non-compliance with Good Clinical Practice (GCP)
- Non-compliance with safety reporting

A listing of all deviations, indicating whether major or minor, will also be included.

9 EFFICACY ANALYSIS

9.1 CHANGE FROM BASELINE IN TUMOUR SIZE

The percentage change from baseline in tumour size at 8-week intervals ($\%\Delta TSz_{timepoint}$) will be defined as follows:

- Baseline tumour size ($TSz_{baseline}$): Sum of longest diameters of target lesions at baseline.
- On-study TSz: Sum of longest diameters of target lesions at a post-treatment disease assessment timepoint.

$$\%\Delta TSz_{timepoint} = 100 \times ((TSz_{timepoint} - TSz_{basline}) / TSz_{baseline})$$

The assessment that happened after the baseline visit will be assigned to the Week 8 timepoint. Further assessments will be sorted by the assessment date, and they will be consecutively assigned with 8-week intervals (Week 16, Week 24 etc.). Unscheduled visits will be taken into account with the date when they were performed.
No visit windowing will be done.

The best percentage change from baseline in tumour size ($\%\Delta TSz_{best}$) across all timepoints will be calculated and presented using waterfall plots.

The $\%\Delta TSz_{best}$ will be defined as follows:

- Baseline tumour size ($TSz_{baseline}$): Sum of longest diameters of target lesions at baseline.
- Best TS (TSz_{best}): Smallest sum of longest diameters of target lesions observed at any timepoint, regardless of whether the assessment was scheduled or unscheduled, after first dose and prior to disease progression.

$$\%\Delta TSz_{best} = 100 \times ((TSz_{best} - TSz_{baseline}) / TSz_{baseline})$$

If a patient with measurable disease has no evaluable post-dose target lesion data then they will be excluded from the waterfall plot of $\%\Delta TSz_{best}$.

Tumour size ($\%\Delta TSz_{Wk8}$ and $\%\Delta TSz_{best}$) will be presented graphically using waterfall plots for presenting each patient's percentage change in tumour size as a separate bar with the bars ordered from the largest increase to the largest decrease. All dose cohorts will be included on the same plot, but different patterns will be used to indicate the dose cohort. Reference lines at the +20% and –30% change in tumour size levels will be added to the plots, which correspond with the definitions of disease progression and partial response (PR) for target lesions, respectively.

9.2 OBJECTIVE RESPONSE RATE

ORR is defined as the number of patients achieving a confirmed response (complete response [CR] or partial response [PR]), defined in accordance with RECIST version 1.1. The number and percentage of patients in each RECIST version 1.1 response category (CR, PR, stable disease [SD], progressive disease [PD] or not evaluable [NE]), as well as the ORR, will be presented by dose cohort.

All data will be listed.

9.3 DISEASE CONTROL RATE

DCR is defined as the number of patients achieving a confirmed response (CR and PR) or SD as a best overall response, defined in accordance with RECIST version 1.1. DCR will be presented by dose cohort if sufficient patients (>3 overall, or >1 per cohort) achieve SD or response.

9.4 DURATION OF RESPONSE

DoR is defined only for the subset of the EFR population patients with a confirmed response of CR or PR, as the time (in days) from the time measurement criteria are first met for CR or PR (whichever is first recorded) until the first date that recurrence or PD is documented. Only responses that were later confirmed will be considered when calculating the DoR.

For patients who were lost to follow-up without progression or reached the timepoint of analysis without known progression or death, the duration of best response (CR, PR or SD) will be censored at the date of the last RECIST version 1.1 assessment.

DoR will be listed. If there are sufficient responders (>3 overall, or >1 per cohort), DoR will be summarised by the number of patients with events, number of censored patients, and the median DoR using the Kaplan-Meier method by dose cohort.

9.5 DURATION OF STABLE DISEASE

Duration of SD for the subset of the EFR population patients with neither sufficient shrinkage to qualify for confirmed PR, nor sufficient increase to qualify for PD, is defined as the time, in days, from the time measurement criteria are first met for SD until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started). For patients who were lost to follow-up without progression or reached the time point of analysis without a known record of death or progression, the duration of SD will be censored at the date of last tumour assessment (RECIST version 1.1).

Duration of SD will be listed. If there are sufficient patients with SD (>3 overall, or >1 per cohort), duration of SD will be summarised by the number of patients with events, number of censored patients, and the median duration of SD using the Kaplan-Meier method by dose cohort.

9.6 PROGRESSION-FREE SURVIVAL

PFS is defined as the time from first dose of study treatment until the date of objective disease progression or death (by any cause in the absence of disease progression) regardless of whether the patient withdraws from study therapy prior to progression. Patients who start another anti-cancer therapy prior to progression will be censored at the date of the last available RECIST version 1.1 assessment.

Patients who have not experienced disease progression or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST version 1.1 assessment.

Disease progression is defined as the progressive disease for target (RSORRES when RSTESTCD =”TRGRESP”) and non-target response (RSORRES when RSTESTCD =”NTRGRESP”) or new lesion occurred (RSORRES=’Y’ when RETESTCD=’NEWLIND’) as reported by investigator.

The PFS time will always be derived based on the scan/assessment dates rather than visit dates and the following rules will be applied:

- Date of objective disease progression will be determined based on the earliest of the dates of the component that triggered the disease progression, i.e., if both the target lesions and the non-target lesions indicate disease progression but were scanned on different days, the earlier of the 2 dates would be applied.
- When censoring a patient for PFS the patient will be censored at the latest of the dates contributing to a particular overall visit assessment

PFS will be presented using all available data up until the earlier of progression and starting subsequent therapy, or last evaluable RECIST version 1.1 assessment in the absence of progression.

The number of overall censored patients, number of patients with events and median PFS using the Kaplan-Meier method will be presented by dose cohort. In addition, the results will be presented graphically in Kaplan-Meier plots. PFS will be analysed using safety population.

9.7 OVERALL SURVIVAL

OS is defined as the time from Screening to the time of death due to any cause.

For patients who are alive at the time of analysis, or are permanently lost to follow-up, duration of OS will be censored at the date at which they were last known to be alive. The date at which the patient is last known to be alive is defined as the latest date of: (i) last site visit; (ii) last date at which the patient had a radiographic scan; and (iii) last date at which the patient, the study investigator, their other physicians, or a family member confirmed that the patient was alive.

The number of overall censored patients, number of patients with events and Kaplan-Meier estimates with 95% confidence intervals will be presented.

9.8 PHARMACODYNAMIC ENDPOINTS (PART 1 ONLY)

Baseline and post-dose PBMC marker data will be analysed using a paired t test by dose cohort. Boxplots for the change from baseline over time in neutrophils, platelets, and lymphocytes will

also be produced. The estimated change from baseline and standard error and associated 95% confidence interval for the change will be presented for each visit.

9.9 PERFORMANCE STATUS

ECOG performance status will be summarised with descriptive statistics by category and dose cohort. A listing of performance status will also be included.

9.10 INTERIM ANALYSIS

Not applicable.

10 SAFETY

The safety population (see section 5.1) will be used for all the analyses of safety data.

10.1 DOSE LIMITING TOXICITY

DLT is defined as any of the following occurring during the first 28-day treatment cycle that are not due to CRC or to a known concurrent medical condition and are judged as clinically significant and related to study treatment, the flag from the investigator will be used.

- Grade 4 neutropaenia (absolute neutrophil count [ANC] $<0.5x10^9$/L) that persists for more than 7 days
- Febrile neutropaenia (ANC $<1000/mm^3$ with a single temperature of >38.3°C [101°F] or a sustained temperature of ≥38°C [100.4°F] for >1 hour)
- Grade 3 thrombocytopaenia (platelets $<50.0x10^9$/L) with bleeding complications requiring platelet transfusions or that persists for more than 7 days
- Grade 4 thrombocytopaenia
- Grade 4 anaemia unexplained by underlying disease
- Grade 5 haematological toxicity
- Grade 4 diarrhoea or vomiting that persists despite optimal medical management
- Grade 3 or greater aspartate aminotransferase (AST)/alanine aminotransferase (ALT) elevation (exceptions may be made for transient [<7 days] Grade 3 elevations of AST/ALT in the presence of known liver metastases and without evidence of other hepatic injury, if agreed by the treating physician and the DSMC)
- Grade 2 or greater AST/ALT elevation and Grade 2 or greater bilirubin elevation (exceptions may be made for transient [<7 days] elevations of AST/ALT and bilirubin in the presence of known liver metastases without evidence of other hepatic injury, if agreed upon by the treating physician and the DSMC)
- Any prolonged toxicity that does not resolve to ≤ Grade 1 or baseline within 21 days of dose interruption
- Any other non-haematological toxicity Grade ≥3 except for:
  - Alopecia

- Grade 3 nausea, vomiting, or diarrhoea events that resolve within 72 hours with anti-emetic or anti-diarrhoeal therapy

The number and percentage of patients within each cohort with any DLTs, and with each DLT, will be provided. All DLT data will be provided in data listings.

10.2 EXPOSURE TO STUDY DRUG

Descriptive statistics for patients treated, including the number of infusions received, total dose given, and infusions delayed (also included infusions administered earlier than scheduled) or missed, will be presented by dose cohort.

To understand the impact of dose reductions on the intended dosing regimen, dose intensity will also be listed and summarised.

Dose intensity for all treatments will be defined as the percentage of the actual cumulative dose delivered, relative to the intended cumulative dose, until the earliest of treatment discontinuation or study discontinuation or last day prior to progression as defined by RECIST v1.1.

To account for the intermittent dosing, the intended cumulative dose will be assumed to be:
For NUC-3373, leucovorin, oxaliplatin, irinotecan, bevacizumab, cetuximab and panitumumab (days 1 and 15 of a 28-day cycle):

- Days 1-14 of a cycle – the intended cumulative dose after dose on day 1 of the cycle is given.
- Days 15-28 of a cycle – the intended cumulative dose after dose on day 15 of the cycle is given.

For cetuximab (days 1, 8, 15 and 22 of a 28-day cycle):

- Days 1-7 of a cycle – the intended cumulative dose after dose on day 1 of the cycle is given.
- Days 8-14 of a cycle – the intended cumulative dose after dose on day 8 of the cycle is given.
- Days 15-21 of a cycle – the intended cumulative dose after dose on day 15 of the cycle is given.
- Days 22-28 of a cycle – the intended cumulative dose after dose on day 22 of the cycle is given.

All exposure and compliance data will be provided in data listings.

10.3 ADVERSE EVENTS

All reported terms (Investigator descriptions) for AEs will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA). Summaries will include TEAEs only. AEs will be considered treatment-emergent if they start on or after the time of the first dose of study treatment and up to 30 days after the last dose of study treatment.

TEAEs will be summarised with frequencies and percentages by dose cohort, system organ classification (SOC), and preferred term.

The following summaries will be produced by dose cohort for all TEAEs:

- An overview table of the incidence of TEAEs, Grade 3 or higher TEAEs, , treatment-related TEAEs, TEAEs leading to treatment discontinuation, TEAEs leading to treatment interruption and TEAEs leading to death, by dose cohort and overall for each combination.
- Summary of TEAEs by SOC and preferred term: Both the number and percentage of patients in each category (patient-level summary) and the number of episodes (episode-level summary).
- Summary of TEAEs occurring in at least 10% of patients by preferred term, sorted in descending order of frequency (*i.e.* most frequent event shown first). The order of frequency will be determined by the most frequent preferred term across all cohorts.
- Summary of CTCAE Grade 3 and above TEAEs by preferred term.
- Summary of CTCAE Grade 3 and above related TEAEs by preferred term
- Summary of treatment-related TEAEs by SOC and preferred term to each study treatment.
- Summary of TEAEs leading to NUC-3373 interruptions by SOC and preferred term.
- Summary of TEAEs leading to treatment discontinuation by SOC and preferred term for each study treatment.
- Summary of TEAEs by SOC, preferred term and maximum severity.
- Summary of TEAEs by SOC, preferred term and worst-case relationship attribution.
- Summary of serious TEAEs by SOC and preferred term
- Summary of serious TEAEs by preferred term sorted in descending order of frequency
- Summary of non-serious TEAEs (excluding SAEs)

Additionally, the following will be listed:

- All AEs, listed with the date of onset, study day, dose at onset, treatment status at onset (pre-treatment, ongoing or post-treatment) and Investigator's assessment of severity and relationship to study drug.
- AEs with outcome of death along with the date of onset, study day, dose at onset, treatment status at onset (pre-treatment, ongoing or post-treatment) and Investigator´s assessment of severity and relationship to study drug.
- All serious TEAEs along with the date of onset, study day, dose at onset, treatment status at onset (pre-treatment, ongoing or post-treatment), date of resolution (if SAE is resolved), Investigator´s assessment of severity and relationship to study drug.
- AEs leading to discontinuation of study medication, listed along with the date of onset, study day, dose at onset, treatment status at onset (pre-treatment, ongoing or post-treatment) and Investigator's assessment of severity and relationship to study drug.
- AEs leading to treatment interruptions, listed along with the date of onset, study day, dose at onset, treatment status at onset (pre-treatment, ongoing or post-treatment) and Investigator's assessment of severity and relationship to study drug.

If an AE is reported more than once during the study period the greatest severity and the worst-case attribution will be presented in summary tables. Any AEs commencing >30 days after discontinuation of study treatment will not be included in the tabulation of AE data.

10.4 SERIOUS ADVERSE EVENTS AND DEATH

Summaries of SAEs will include treatment-emergent SAEs only. Serious TEAEs will be summarised with frequencies and percentages by dose cohort, SOC, and preferred term.

The following summaries will be produced by dose cohort for all serious TEAEs:

- Summary of SAEs by SOC and preferred term
- Summary of Related SAEs by SOC and preferred term
- Summary of SAEs by preferred term sorted in descending order of frequency.

All SAEs will be listed along with the date of onset, study day, dose at onset, treatment status at onset (pre-treatment, ongoing or post-treatment), date of resolution (if SAE is resolved), Investigator's assessment of severity and relationship to study drug.

A summary of all deaths will be provided.

A summary of TEAEs with outcome of death will also be presented.

AEs with outcome of death will be listed along with the date of onset, study day, dose at onset, treatment status at onset (pre-treatment, ongoing or post-treatment) and Investigator's assessment of severity and relationship to study drug.

10.5 LABORATORY EVALUATIONS

For laboratory assessments with a result below a certain limit, the analysis value will be set to half of the numeric value. Furthermore, the values starting with ">" will be set to the numeric value without ">".

Laboratory assessments at screening, C0D1 in Part 1a and 1b or C1D1 in all other cohorts, baseline and each scheduled visit and change from baseline at each post-baseline scheduled visit will be summarised with descriptive statistics by panel, test, dose cohort, and time point for continuous data. For categorical data, shifts from baseline at each post-baseline scheduled visit will be presented by panel, test, dose cohort, and time point. Additionally, abnormal results will be summarised with frequencies and percentages by clinical significance, panel, test, treatment group, and time point.
Boxplots and spaghetti plots for the change from baseline over time in ALT, AST, bilirubin, neutrophils, platelets, and lymphocytes will also be produced by dose cohort.

To enable assessment for the potential for drug induced liver injury, the following outputs will be produced:

- A scatter plot of maximum on-treatment alanine aminotransferase (ALT) versus maximum on-treatment total bilirubin, both expressed as multiples of the upper limit of normal (ULN), including reference lines at 3xULN for ALT and 2xULN for total bilirubin.

- A scatter plot of maximum on-treatment aspartate aminotransferase (AST) versus maximum on-treatment total bilirubin, both expressed as multiples of the upper limit of normal (ULN), including reference lines at 3xULN for AST and 2xULN for total bilirubin.

The maximum values for ALT, AST and total bilirubin may occur at different visits.

In the event that the scatter plots identify any potential Hy's law cases (ALT>3xULN and total bilirubin>2xULN, or AST>3xULN and total bilirubin>2xULN), profile plots over time for such cases will be provided for the patient's liver function tests (ALT, AST, total bilirubin and alkaline phosphatase) expressed in multiples of ULN with all four endpoints on the same plot.

Data listings will display all laboratory test results and findings.

10.6 VITAL SIGNS

Actual values at baseline and each scheduled visit and change from baseline at each post-baseline scheduled visit of vital signs (including pulse, respiration, systolic and diastolic blood pressure, oral temperature, and weight) will be summarised with descriptive statistics by dose cohort and time point. A data listing of all data will also be included.

10.7 ELECTROCARDIOGRAMS

ECG parameters will be described at each timepoint. The site will be required to review ECGs as a safety check. This will be done immediately by a qualified Investigator or cardiologist at the study site. ECG assessments may be retained for review centrally, where results will be provided to the study site and retained as source data.

The triplicate values at each timepoint for a patient will be averaged, and the average value will be used in the summaries. Actual values at baseline and each scheduled visit and change from baseline at each post-baseline scheduled visit in ECG endpoints will be summarised with descriptive statistics by dose cohort and time point. Additionally, abnormal results will be summarised with frequencies and percentages by clinical significance, treatment group, and time point. All ECG data will be displayed in a data listing.

The Holter ECG will also be analyzed at each timepoint in addition and the change from baseline will not be presented due to no baseline value.

10.8 PHYSICAL EXAMINATIONS

A data listing of all results will be provided.

11 PHARMACOKINETIC ANALYSES

The pharmacokinetic analysis is outside the scope of this analysis plan.

12 OTHER ANALYSES

Not applicable.

13 PRIMARY AND FINAL ANALYSES

13.1 COHORT ANALYSES

The analysis of safety for a cohort will take place when all of the enrolled patients have completed one treatment cycle or have withdrawn from treatment. At least 3 evaluable patients are required for the analysis. The efficacy analysis of % change in tumour size will take place when all patients in a given cohort have undergone at least 2 imaging assessments for evaluation of percentage change in tumour size by RECIST v1.1, or have withdrawn from treatment.

13.2 END OF STUDY ANALYSIS

A final analysis will be conducted after the last patient completes or discontinues the study and the resulting clinical database has been cleaned, quality checked, and locked.

14 TABLE OF CONTENTS FOR DATA DISPLAYS

14.1 DEMOGRAPHICS SUMMARY FIGURES AND TABLES

14.2 EFFICACY SUMMARY FIGURES AND TABLES

14.2.1 Efficacy Tables

Table	Title	Population
14.2.1.1	Summary of Percentage Change from Baseline in Tumour Size (mm) over time	EFR Population
14.2.1.2	Summary of Best Percentage Change from Baseline in Tumour Size (mm)	EFR Population
14.2.2	Summary of Best RECIST Response	EFR Population
14.2.3	Summary of Duration of Response	EFR Population
14.2.4	Summary of Duration of Stable Disease	EFR Population
14.2.5.1	Summary of Progression Free Survival	Safety Population
14.2.6.1	Summary of Overall Survival	FAS Population
14.2.7	Summary of Pharmacodynamic Data	FAS Population
14.2.8	Summary of ECOG Performance Status	Safety Population

14.2.2 Efficacy Figures

Figure	Title	Population
14.2.1.3	Waterfall Plot of Percentage Change from Baseline in Tumour Size at Week 8	EFR Population
14.2.1.4	Waterfall Plot of Best Percentage Change from Baseline in Tumour Size	EFR Population
14.2.5.2	Kaplan-Meier Plot of Progression Free Survival	Safety Population
14.2.6.2	Kaplan-Meier Plot of Overall Survival	FAS Population

14.3 SAFETY SUMMARY FIGURES AND TABLES

14.3.1 Adverse Events

Table	Title	Population
14.3.1.1	Summary of Dose Limiting Toxicities	Safety Population
14.3.1.2	Overall Summary of Adverse Events	Safety Population
14.3.1.3.1	Summary of Treatment Emergent Adverse Events by System Organ Classification and Preferred Term – Patient Level	Safety Population
14.3.1.3.2	Summary of Treatment Emergent Adverse Events by System Organ Classification and Preferred Term – Episode Level	Safety Population
14.3.1.4.1	Summary of Most Frequent (>10% Overall) Treatment Emergent Adverse Events by Preferred Term (part 1 and arm 2a-b)	Safety Population
14.3.1.4.2	Summary of Most Frequent (>10% Overall) Treatment Emergent Adverse Events by Preferred Term (arm 2c)	Safety Population
14.3.1.4.3	Summary of Most Frequent (>10% Overall) Treatment Emergent Adverse Events by Preferred Term (arm 2d)	Safety Population
14.3.1.4.4	Summary of Most Frequent (>10% Overall) Treatment Emergent Adverse Events by Preferred Term (arm 3a)	Safety Population
14.3.1.4.5	Summary of Most Frequent (>10% Overall) Treatment Emergent Adverse Events by Preferred Term (arm 3b)	Safety Population
14.3.1.4.6	Summary of Most Frequent (>10% Overall) Treatment Emergent Adverse Events by Preferred Term (arm 3c)	Safety Population
14.3.1.4.7	Summary of Most Frequent (>10% Overall) Treatment Emergent Adverse Events by Preferred Term (arm 3d)	Safety Population
14.3.1.4.8	Summary of Most Frequent (>10% Overall) Treatment Emergent Adverse Events by Preferred Term (arm 3e)	Safety Population
14.3.1.4.9	Summary of Most Frequent (>10% Overall) Treatment Emergent Adverse Events by Preferred Term (arm 3f)	Safety Population
14.3.1.4.10	Summary of Most Frequent (>10% Overall) Treatment Emergent Adverse Events by Preferred Term (arm 3g)	Safety Population
14.3.1.5.1	Summary of Treatment Emergent Adverse Events Grade 3 or Higher by System Organ Classification and Preferred Term	Safety Population
14.3.1.5.2	Summary of Related Treatment Emergent Adverse Events Grade 3 or Higher by System Organ Classification and Preferred Term	Safety Population
14.3.1.6.1	Summary of NUC-3373 Related Treatment Emergent Adverse Events by System Organ Classification and Preferred Term	Safety Population
14.3.1.6.2	Summary of Leucovorin Related Treatment Emergent Adverse Events by System Organ Classification and Preferred Term	Safety Population

14.3.1.6.3	Summary of Oxaliplatin Related Treatment Emergent Adverse Events by System Organ Classification and Preferred Term	Safety Population
14.3.1.6.4	Summary of Irinotecan Related Treatment Emergent Adverse Events by System Organ Classification and Preferred Term	Safety Population
14.3.1.6.5	Summary of Bevacizumab Related Treatment Emergent Adverse Events by System Organ Classification and Preferred Term	Safety Population
14.3.1.6.6	Summary of Panitumumab Related Treatment Emergent Adverse Events by System Organ Classification and Preferred Term	Safety Population
14.3.1.6.7	Summary of Cetuximab Related Treatment Emergent Adverse Events by System Organ Classification and Preferred Term	Safety Population
14.3.1.7	Summary of Treatment Emergent Adverse Events Leading to NUC-3373 Interruptions by System Organ Classification and Preferred Term	Safety Population
14.3.1.8.1	Summary of Treatment Emergent Adverse Events Leading to NUC-3373 Discontinuation by System Organ Classification and Preferred Term	Safety Population
14.3.1.8.2	Summary of Treatment Emergent Adverse Events Leading to Leucovorin Discontinuation by System Organ Classification and Preferred Term	Safety Population
14.3.1.8.3	Summary of Treatment Emergent Adverse Events Leading to Oxaliplatin Discontinuation by System Organ Classification and Preferred Term	Safety Population
14.3.1.8.4	Summary of Treatment Emergent Adverse Events Leading to Irinotecan Discontinuation by System Organ Classification and Preferred Term	Safety Population
14.3.1.8.5	Summary of Treatment Emergent Adverse Events Leading to Bevacizumab Discontinuation by System Organ Classification and Preferred Term	Safety Population
14.3.1.8.6	Summary of Treatment Emergent Adverse Events Leading to Panitumumab Discontinuation by System Organ Classification and Preferred Term	Safety Population
14.3.1.8.7	Summary of Treatment Emergent Adverse Events Leading to Cetuximab Discontinuation by System Organ Classification and Preferred Term	Safety Population
14.3.1.9	Summary of Treatment Emergent Adverse Events by System Organ Classification, Preferred Term and Maximum Severity	Safety Population
14.3.1.10	Summary of Treatment Emergent Adverse Events by System Organ Classification, Preferred Term and Worst-Case Relationship	Safety Population

14.3.1.11	Summary of non-serious Treatment Emergent Adverse Events by System Organ Classification, Preferred Term	Safety Population
14.3.1.12	Summary of Treatment Emergent Adverse Events with outcome of death by System Organ Classification, Preferred Term	Safety Population

14.3.2 Serious Adverse Events, Deaths and Other Significant Adverse Events

Table	Title	Population
14.3.2.1	Summary of Serious Treatment Emergent Adverse Events by System Organ Classification and Preferred Term	Safety Population
14.3.2.2	Summary of Related Serious Treatment Emergent Adverse Events by Preferred Term	Safety Population
14.3.2.3	Summary of Deaths by System Organ Classification and Preferred Term	Safety Population

14.3.3 Narratives

Not covered in this SAP and will be provided in the CSR.

14.3.4 Laboratory Results

Table	Title	Population
14.3.4.1.1	Summary of Chemistry Results	Safety Population
14.3.4.1.2	Summary of Abnormal Chemistry Results	Safety Population
14.3.4.2.1	Summary of Haematology Results	Safety Population
14.3.4.2.2	Summary of Abnormal Haematology Results	Safety Population
14.3.4.3.1	Summary of Coagulation Results	Safety Population
14.3.4.3.2	Summary of Abnormal Coagulation Results	Safety Population
14.3.4.4.1	Summary of Urinalysis Results	Safety Population
14.3.4.4.2	Summary of Abnormal Urinalysis Results	Safety Population
14.3.4.4.3	Summary of Urinalysis Results Shifts From Baseline	Safety Population
14.3.4.5	Summary of Pregnancy Test Results	Safety Population

14.3.5 Laboratory Figures

Figure	Title	Population
14.3.4.1.3	Boxplots of Chemistry Results	Safety Population
14.3.4.1.4	Spaghetti Plots of Chemistry Results	Safety Population
14.3.4.2.3	Boxplots of Haematology Results	Safety Population
14.3.4.2.4	Spaghetti Plots of Haematology Results	Safety Population
14.3.4.6.1	Scatter Plot of Maximum ALT vs Maximum Total Bilirubin	Safety Population
14.3.4.6.2	Scatter Plot of Maximum AST vs Maximum Total Bilirubin	Safety Population
14.3.4.6.3.x	Hys Law Plot for Patient XXX-XXX	Safety Population

14.4 OTHER SUMMARY FIGURES AND TABLES

Table	Title	Population
14.4.1	Summary of Vital Signs Results	Safety Population
14.4.2	Summary of ECG Results	Safety Population
14.4.3	Summary of Abnormal ECG Results	Safety Population

14.5 PK SUMMARY FIGURES AND TABLES

To be provided in a separate stand-alone PK report.

14.6 LISTINGS

16.2.1 Discontinued Patients

16.2.1.1 Listing of Patient Disposition

16.2.2 Protocol Deviations

16.2.2.1 Listing of Inclusion/Exclusion Criteria Deviations

16.2.2.2 Listing of Protocol Violations and Deviations

16.2.3 Patients Excluded from the Efficacy Analysis

16.2.3.1 Listing of Analysis Populations

16.2.4 Demographic Data

16.2.4.1 Listing of Demographics

16.2.4.2 Listing of Cancer Diagnosis

16.2.4.3 Listing of Prior and Concomitant Medications
16.2.4.4 Listing of Prior and Concomitant Procedures
16.2.4.5 Listing of Prior Chemotherapy Treatment
16.2.4.6 Listing of Prior Radiation Therapy
16.2.4.7 Listing of Prior Surgical Therapy
16.2.4.8 Listing of Medical History
16.2.4.9 Listing of RAS Status
16.2.4.10 Listing of BRAF Status
16.2.4.11 Listing of Archival Tumour Sample
16.2.4.12 Listing of Tumour Biopsy Sample

16.2.5 Compliance and/or Drug Concentration Data

16.2.5.1 Listing of Exposure to NUC-3373
16.2.5.2 Listing of NUC-3373 Dose Intensity
16.2.5.3 Listing of Exposure to Leucovorin
16.2.5.4 Listing of Leucovorin Dose Intensity
16.2.5.5 Listing of Exposure to Oxaliplatin
16.2.5.6 Listing of Oxaliplatin Dose Intensity
16.2.5.7 Listing of Exposure to Irinotecan
16.2.5.8 Listing of Irinotecan Dose Intensity
16.2.5.9 Listing of Exposure to Bevacizumab
16.2.5.10 Listing of Bevacizumab Dose Intensity
16.2.5.11 Listing of Exposure to Panitumumab
16.2.5.12 Listing of Panitumumab Dose Intensity
16.2.5.13 Listing of Exposure to Cetuximab
16.2.5.14 Listing of Cetuximab Dose Intensity

16.2.6 Individual Efficacy Response Data

16.2.6.1 Listing of Tumour Assessments
16.2.6.2 Listing of RECIST Response by Visit
16.2.6.3 Listing of Best RECIST Response
16.2.6.4 Listing of Duration of Response and Stable Disease
16.2.6.5 Listing of Progression Free Survival
16.2.6.6 Listing of Overall Survival
16.2.6.7 Listing of ECOG Performance Status
16.2.6.8 Listing of Biomarker Results

16.2.7 Adverse Event Listings

16.2.7.1 Listing of All Adverse Events
16.2.7.2 Listing of Adverse Events Leading to Discontinuation from Treatment
16.2.7.3 Listing of Adverse Events Leading to Treatment Interruptions
16.2.7.4 Listing of Adverse Events Leading to Death
16.2.7.5 Listing of Serious Adverse Events
16.2.7.6 Listing of Deaths
16.2.7.7 Listing of Dose Limiting Toxicities

16.2.8 Listings of Individual Laboratory Measurements

16.2.8.1 Definitions of Normal Ranges for Laboratory Values
16.2.8.2 Listing of Chemistry Results
16.2.8.3 Listing of Abnormal Chemistry Results
16.2.8.4 Listing of Haematology Results
16.2.8.5 Listing of Abnormal Haematology Results
16.2.8.6 Listing of Coagulation Results
16.2.8.7 Listing of Abnormal Coagulation Results
16.2.8.8 Listing of Urinalysis Results
16.2.8.9 Listing of Abnormal Urinalysis Results
16.2.8.10 Listing of CEA Results
16.2.8.11 Listing of Pregnancy Testing Results

16.2.9 Other Listings

16.2.9.1 Listing of Vital Signs Test Results
16.2.9.2 Listing of Electrocardiogram Findings
16.2.9.3 Listing of Physical and Neurological Examinations
16.2.9.4 Listing of Initial Pregnancy Report (only to be presented if any pregnancies)
16.2.9.5 Listing of Pregnancy Follow Up Report (only to be presented if any pregnancies)

15 REFERENCES

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Uppsala Monitoring Centre (https://www.who-umc.org/whodrug/whodrug-portfolio#)

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