



CLINICAL STUDY PROTOCOL: MODULE 2

NUC-3373 in combination with docetaxel for the treatment of patients with non-small cell lung cancer or pleural mesothelioma

IMPs	NUC-3373 & docetaxel
Protocol Number: Module	NuTide:303: Module 2
Protocol Version, Date	Version 2.2, 15 January 2024
Development Phase	Ib/II
IND Number	135275
EudraCT Number	2022-000722-14
NCT Number	NCT05714553
Sponsor:	NuCana plc 3 Lochside Way Edinburgh, EH12 9DT, UK Telephone: +44 (0)131 357 1111 Email: Nutide303@nucana.com

Approval:

	_____ Dr Elisabeth Oelmann, MD PhD	_____ Date
	SVP, Medical & Clinical Development	
Medical Monitor:	Elisabeth Oelmann NuCana plc 3 Lochside Way, Edinburgh, EH12 9DT, UK Tel: +44 (0) 131 357 1118	

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PRINCIPAL INVESTIGATOR AGREEMENT AND SIGNATURE

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This study will be conducted in compliance with the clinical study protocol (and amendments), International Council for Harmonisation guidelines for current Good Clinical Practice (ICH-GCP) and applicable regulatory requirements. Compliance with ICH-GCP standards provides assurance that the rights, safety, and wellbeing of study patients are protected, consistent with the principles that have their origin in the Declaration of Helsinki.

Principal Investigator's signature

Date (dd-mmm-yyyy)

Principal Investigator's name (printed)

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MODULE 2 SYNOPSIS

Study Title	A Phase Ib/II open label, multi-arm, parallel cohort dose finding and expansion study to assess the safety, pharmacokinetics and efficacy of NUC-3373, a nucleotide analogue, given in combination with other agents in patients with advanced solid tumours
Module Title	NUC-3373 in combination with docetaxel for the treatment of patients with non-small cell lung cancer or pleural mesothelioma
Protocol Number	NuTide:303
IND Number	135275
EudraCT Number	2022-000722-14
NCT Number	NCT05714553
Phase	Ib/II
Objectives	Primary Objectives <u>Phase Ib: Dose-validation phase</u> To determine the maximum tolerated dose (MTD) and the overall safety profile of NUC-3373 + leucovorin (LV) in combination with docetaxel. <u>Phase II: Dose-expansion phase</u> To evaluate the preliminary anti-tumour activity of NUC-3373 + LV in combination with docetaxel. Secondary Objectives • To evaluate the anti-tumour activity of NUC-3373 + LV in combination with docetaxel (Phase Ib) • To further evaluate the safety profile of NUC-3373 + LV in combination with docetaxel (Phase Ib and II) • To evaluate the pharmacokinetics (PK) of NUC-3373 and metabolites (Phase Ib and II)
Study Design	Multi-centre, open-label, multi-arm, parallel cohort, dose validation and expansion design. The study is modular in design, allowing evaluation of the safety, efficacy and PK of NUC-3373 in combination with other agents for the treatment of patients with different tumour types. The study includes a number of modules, each evaluating a different NUC-3373 combination. Each module of this study consists of a dose-validation phase (Phase Ib) and a dose-expansion phase (Phase II). This module (Module 2) will assess NUC-3373 + LV in combination with docetaxel for the treatment of patients with advanced/metastatic non-small cell lung cancer (NSCLC) or pleural mesothelioma who have progressed on, or were unable to tolerate, 1 or 2 prior lines of cytotoxic chemotherapy-containing regimens for advanced/metastatic disease.

	Phase Ib: In Phase Ib (dose-validation), approximately 6-12 evaluable patients will be enrolled in a 3+3 dose escalation design to determine the recommended dose for NUC-3373 + LV in combination with docetaxel. The exact number of patients will depend upon the number of dose escalation steps required to determine a recommended dose. Phase II: Phase II (dose expansion) will further evaluate the combination using a Simon's two-stage design. In the first stage, 13 patients will be accrued. If there are no responses in these 13 patients, the cohort will be stopped. Otherwise, 14 additional patients will be accrued for a total of 27 patients.
Study Centres	This module will be conducted at approximately 2-15 sites in the United Kingdom and/or United States.
Endpoints	<u>Primary Endpoints</u> <u>Phase Ib: Dose-validation phase</u> • MTD for NUC-3373 + LV in combination with docetaxel • Safety, as assessed by treatment-emergent adverse events (TEAEs), clinically significant laboratory changes, and changes in physical exam, vital signs and serial electrocardiograms (ECGs) <u>Phase II: Dose-expansion phase</u> • Objective response rate (ORR), defined as the percentage of patients achieving a confirmed complete or partial response to treatment, based on Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 criteria <u>Secondary Endpoints</u> Efficacy (Phase Ib and 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 based on: • Maximum percentage change from baseline in tumour size • ORR (Phase Ib only) • Disease Control Rate (DCR) • Duration of Response (DoR) • Duration of Stable Disease (DoSD) • Progression-Free Survival (PFS) • Overall Survival (OS) Safety (Phase II) • TEAEs (per Common Terminology Criteria for Adverse Events [CTCAE] v5.0) • Clinically significant laboratory changes (per CTCAE v5.0) • Changes in physical exam, vital signs and serial ECGs

	Pharmacokinetics (Phase Ib and II) The PK of NUC-3373 will be assessed, including: • Concentration at end of NUC-3373 infusion (C_{inf}) • Maximum concentration (C_{max}) • Area under the plasma concentration-time curve (AUC) • Half-life ($t_{1/2}$) • Volume of distribution (V_d) • Clearance (CL) The analytes measured in plasma may include, but are not limited to: NUC-3373, 5-fluorouracil (5-FU), α-fluoro-β-alanine (FBAL), deoxyuridine (dUrd).
Study Population	Patients with a confirmed diagnosis of NSCLC or pleural mesothelioma that is radiologically measurable, with evidence of locally advanced/unresectable or metastatic disease; Eastern Cooperative Oncology Group (ECOG) performance status 0-1; adequate haematologic, renal and hepatic function.
Study Treatment	NUC-3373 will be administered at a starting dose of 750 mg/m ² in combination with LV at a dose of 400 mg/m ² and docetaxel at a starting dose of 55 mg/m ² . Dose escalation of NUC-3373 and docetaxel will be performed using a modified 3+3 design. NUC-3373 and LV will be administered on Days 1 and 22 and docetaxel will be administered on Day 8 of 28-day cycles. The dosing schedule may be adjusted based on emerging data with agreement from the Safety Review Committee.
Sample Size	It is anticipated that approximately 6-12 patients will be enrolled in Phase Ib and 13-27 patients will be enrolled in Phase II in this module.
Inclusion Criteria	1. Provision of written informed consent. 2. Confirmed diagnosis of NSCLC (any histology) or pleural mesothelioma (any histology) with evidence of locally advanced/unresectable or metastatic disease. 3. Must have progressed on, or were unable to tolerate, 1 or 2 prior lines of cytotoxic chemotherapy-containing standard of care regimens for advanced/metastatic disease (not including neoadjuvant or adjuvant therapy). Additional prior lines of treatment with targeted agents or immunotherapy are allowed as long as they were not given in combination with cytotoxic chemotherapy. Prior regimens in which one drug is substituted for another due to toxicity count as 1 line of treatment. Prior treatment with docetaxel for metastatic disease is not allowed, see exclusion criterion 6. 4. Age ≥ 18 years. 5. Minimum life expectancy of ≥ 12 weeks. 6. ECOG performance status 0 or 1. 7. Measurable disease as defined by RECIST v1.1.

	8. Adequate bone marrow function as defined by absolute neutrophil count (ANC) $\geq 1.5 \times 10^9/\text{L}$, platelet count $\geq 100 \times 10^9/\text{L}$ (with no evidence of bleeding), and haemoglobin $\geq 9 \text{ g/dL}$. 9. Adequate liver function, as defined by serum total bilirubin < upper limit of normal (ULN), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leq 2.5 \times \text{ULN}$ (or $\leq 5 \times \text{ULN}$ if liver metastases are present). In the event of concomitantly increased ALP values $> 2.5 \times \text{ULN}$, AST and ALT must be $< 1.5 \times \text{ULN}$. 10. Adequate renal function assessed as serum creatinine $< 1.5 \times \text{ULN}$ and glomerular filtration rate $\geq 50 \text{ mL/min}$ (calculated by the Cockcroft-Gault method). 11. Serum albumin $\geq 3 \text{ g/dL}$. 12. Ability to comply with protocol requirements. 13. Female patients of child-bearing potential must have a negative pregnancy test within 7 days prior to the first study drug administration. This criterion does not apply to patients who have had a previous hysterectomy or bilateral oophorectomy. Male patients and female patients of child-bearing potential must agree to practice true abstinence or to use two forms of contraception, one of which must be highly effective. These forms of contraception must be used from the time of signing consent, throughout the treatment period, and for 6 months following the last dose of any study medication. Oral or injectable contraceptive agents cannot be the sole method of contraception. 14. Patients must have been advised to take measures to avoid or minimize exposure to UV light for the duration of study participation and for a period of 4 weeks following the last dose of study medication.
Exclusion Criteria:	1. History of hypersensitivity or current contra-indications to 5-FU, floxuridine (FUDR), capecitabine (refer to latest package inserts), or the components of the NUC-3373 drug product formulation (super refined polysorbate 80 [SRP80], dimethylacetamide [DMA]). 2. Prior history of hypersensitivity or current contra-indication to docetaxel, polysorbate 80, ethanol (anhydrous) or citric acid. 3. Residual toxicities from prior chemotherapy, immunotherapy or radiotherapy which have not regressed to Grade ≤ 1 severity (CTCAE v5.0), except for alopecia, peripheral neuropathy and ototoxicity (which are excluded if $\geq$ Grade 3). 4. Total serum bilirubin $> \text{ULN}$ and/or AST and ALT $\geq 1.5 \times \text{ULN}$ together with concomitantly increased ALP values $> 2.5 \times \text{ULN}$ 5. Chemotherapy, hormonal therapy, radiotherapy (other than a short cycle of palliative radiotherapy, e.g., for bone pain*), immunotherapy, biological agents, or exposure to another investigational agent within 21 days (or four times the half-life for molecular targeted agents, whichever is shorter) of first administration of study treatment: a. For nitrosoureas and mitomycin C within 6 weeks of first administration of NUC-3373 b. Corticosteroid treatment is allowed during screening but should be weaned to a dose of 10 mg prednisolone (or steroid equivalent) by Cycle 1 Day 1

	<i>* Palliative radiotherapy during participation in the study is permitted, but should not be concurrent with study treatment and recovery should be allowed to prevent overlapping toxicity. It should not include a target lesion.</i> 6. Patients who have received >2 prior lines of cytotoxic chemotherapy-containing regimens for advanced/metastatic disease. 7. Patients who have received prior treatment with docetaxel for advanced/metastatic disease. 8. Congenital or acquired immunodeficiency (<i>e.g.</i>, serious active infection with HIV). Patients with HIV who are healthy and have a low risk of AIDS-related outcomes are eligible. 9. Symptomatic central nervous system or leptomeningeal metastases. 10. Symptomatic ascites, ascites currently requiring drainage procedures or ascites requiring drainage over the 3 months prior to date of first dose of study drug. 11. Uncontrolled concurrent cancer other than the indication under investigation. Patients with a concurrent cancer whose natural history or treatment does not have the potential to interfere with safety or efficacy assessment are eligible. 12. Presence of an active bacterial or viral infection (including SARS-CoV-2, Herpes Zoster or chicken pox), or known active hepatitis B or C. 13. Presence of any uncontrolled concurrent serious illness, medical condition or other medical history, including laboratory results, which, in the Investigator's opinion, would be likely to interfere with the patient's ability to participate in the study or with the interpretation of the results, including any of the following: a. Congestive heart failure (New York Heart Association Class III or Class IV) b. Clinically significant coronary heart disease or myocardial infarction within 6 months of the first dose of study medication or high risk of uncontrolled arrhythmia c. Unstable or poorly controlled angina pectoris d. Complete left bundle branch, bifascicular block or other clinically significant abnormal ECG finding e. QTc interval >470 milliseconds f. History of or current risk factor for torsade de pointes (<i>e.g.</i>, heart failure, hypokalaemia, or a family history of long QT syndrome) g. History of severe skin reactions h. History of severe ocular disorders i. Interstitial pneumonitis or pulmonary fibrosis 14. Any condition (<i>e.g.</i>, known or suspected poor compliance, psychological instability, geographical location, <i>etc.</i>) that, in the judgment of the Investigator, may affect the patient's ability to sign the informed consent and undergo study procedures. 15. Currently pregnant, lactating or breastfeeding. 16. Required concomitant use of drugs known to prolong QT/QTc interval.
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	17. Required concomitant use of strong CYP3A4 inducers or strong CYP3A4 inhibitors. The use of strong CYP3A4 inducers within 2 weeks of first receipt of study drug or the use of strong CYP3A4 inhibitors within 1 week of first receipt of study drug is also excluded. 18. Use of live attenuated vaccines against infectious diseases (e.g., measles mumps rubella [MMR combined vaccines], Rotavirus, Chickenpox, yellow fever) within 4 weeks of initiation of study treatment. 19. Known DPD or TYMP mutations associated with toxicity to fluoropyrimidines. 20. Full-dose anti-coagulation treatment is prohibited. Use of warfarin and other types of long-acting anti-coagulants (such as phenprocoumon and anti-Xa inhibitors with a half-life of >12 hours) is prohibited within 4 weeks of the first dose of study treatment. Patients requiring low dose anti-coagulant treatment should switch to low molecular weight heparin or anti-Xa inhibitors with a half-life of ≤12 hours.
Study Duration Per Patient	Patients may continue to receive treatment in the absence of radiological disease progression or unacceptable toxicity that is not ameliorated by optimal medical or non-medical supportive or prophylactic care, or withdrawal of consent. All patients will be followed up until withdrawal of consent, lost to follow-up, death, or the overall end of study, whichever is earliest.
Sample size and statistical methodology	In Phase Ib, approximately 6-12 evaluable patients will be enrolled in a 3+3 dose escalation design to determine the recommended dose for NUC-3373 + LV in combination with docetaxel. In Phase II, a Simon's two-stage design will be used. The null hypothesis that the true response rate is 5% will be tested against a one-sided alternative. In the first stage, 13 patients will be accrued. If there are no responses in these 13 patients, the cohort will be stopped. Otherwise, 14 additional patients will be accrued for a total of 27 patients. The null hypothesis will be rejected if 4 or more responses are observed in 27 patients. The design yields a type I error rate of 0.04 and power of 0.8 when the true response rate is 20%.

SUMMARY SCHEDULE OF EVENTS: MODULE 2

Study Assessments ¹	Screening/ Baseline	Cycle 1*				Additional Cycles*				End of Treatment	Follow-up Visits	
	D -28 to 0	D1	D8 (±1)	D15 (±1)	D22 (±1)	D1	D8** (±1)	D15 (±1)	D22 (±1)	30 days post last dose (+7 days)	Q8 weeks (±7 days)	Q12 weeks (±14 days)
Informed consent	X											
Inclusion/exclusion criteria	X											
Demographic data	X											
Previous medical history	X											
Concomitant medication	X	X	X	X	X	X	X	X	X	X		
Full physical examination ²	X	X ³				X ^{1,2}				X		
Directed physical examination ²						X ^{1,2}						
Urinalysis	X	X ³				X ¹				X		
ECOG performance status	X	X ³				X ¹				X		
Vital signs ⁴	X	X	X	X	X	X	X	X	X	X		
Weight	X	X				X				X		
Pre-dose ECG ⁵	X	X				X				X		
Post-dose ECG ⁶		X										
Pregnancy test ⁷	X	X ⁷				X				X		
FBC and chemistry ^{1,8}	X	X ³	X	X	X	X	X	X	X	X		
Coagulation profile ¹	X	X ³	X	X	X	X	X	X	X	X		
Radiologic tumour assessment ⁹	X	Assessed every 8 weeks from the start of Cycle 1									X ¹⁰	
Collect prior scan reports ¹¹	Assessed during study participation											
NUC-3373 administration		X			X	X			X			
LV administration		X			X	X			X			
Docetaxel administration ¹²			X				X					
AEs/SAEs ¹³	X	X	X	X	X	X	X	X	X	X		
PK blood sample ¹⁴		X				X ¹⁴						
Follow-up												X ¹⁵

* All cycles are 28 days in duration

** If a patient stops docetaxel treatment for any reason, the Day 8 visit may be performed by telephone call to collect information on AEs and concomitant medications.

- 1 Assessments scheduled on days of dosing should be done prior to administration of all Investigational Medicinal Products (IMPs), unless otherwise specified. Lab assessments, physical examination, and ECOG status may be performed up to 72 hours prior to IMP administration.
- 2 In Phase Ib, a full physical assessment should be completed at C1D1, C2D1 and at End of Treatment. From C3D1 onwards, a directed physical assessment (directed by clinical signs and symptoms) will be completed (in place of the full physical assessment), but only if clinically indicated. In Phase II, a full physical assessment should be completed at C1D1 and End of Treatment only. In all other cycles a directed physical assessment will be completed (in place of the full physical assessment), but only if clinically indicated.
- 3 Does not need to be repeated if Screening assessment was performed within 72 hours of C1D1.
- 4 Vital signs include respiration rate, pulse, temperature and blood pressure. Height should be recorded at baseline only. Weight should be recorded at baseline, Day 1 of every cycle and at end of study visit. If a patient's weight increases or decreases by $\geq 10\%$ during the course of the study, the dose of 'NUC-3373 for infusion' should be recalculated.
- 5 **Pre-dose ECGs:** Standard 12-lead ECG measurements will be performed prior to administration of all IMPs on Day 1 of each cycle. All 12-lead ECG measurements should be reviewed by the Investigator or qualified designee for safety and quality.
- 6 **Post-dose ECGs:** Additional standard 12-lead ECG measurements must be taken post administration of NUC-3373 (end of administration ± 5 minutes) during Cycle 1 only at the C1D1 visit. The ECGs should be reviewed by the Investigator or qualified designee for safety and quality.
- 7 Serum pregnancy assessment to be performed within 7 days of C1D1. Required only in women of childbearing potential.
- 8 Clinical chemistry (including hepatic panel) and haematology will be conducted weekly throughout the study. In the event of neutropenia ($ANC < 0.5 \times 10^9/L$), thrombocytopenia (platelet count $< 50 \times 10^9/L$), or $\geq$ Grade 2 clinical chemistry toxicity, these assessments will be conducted more frequently as clinically indicated until toxicity resolves to $\leq$ Grade 1.
- 9 Computed tomography (CT)/magnetic resonance imaging (MRI) disease assessments will be performed at Screening (within 28 days prior to the first dose of IMP) and every 8 weeks (± 7 days) from C1D1. Additional tests may be requested at the Investigator's discretion.

CRs and PRs must be confirmed by repeated measurement. The confirmatory scans should be performed at least 28 days and not more than 42 days after initial assessment of response.

If a patient is found to have a response at the confirmatory scan which has improved from PR to CR, then the improved response must also be confirmed within a further 28- to 42-day window.

The same modality should be used throughout.
- 10 Patients withdrawing from study treatment with no radiological evidence of disease progression will remain in the study and receive scans every 8 weeks (± 7 days) from C1D1 until disease progression, initiation of a new treatment or death, in order to determine duration of overall response and PFS. Patients who stop treatment following an unconfirmed response should also still have a confirmatory scan within the pre-specified 28- to 42-day window, if the scan can take place prior to the patient starting any subsequent anti-cancer therapies.
- 11 Collection of prior scan reports for assessment of previous tumour measurements can be performed any time during patient participation in the study or during follow-up. This will allow understanding of the trajectory of tumour growth prior to the patient entering this study.

- 12** Prophylactic G-CSF support is required during all cycles of treatment and should be administered in line with standard institutional practice. It is recommended that pegfilgrastim is given on Day 10 of each cycle; however, alternative agents may be discussed with the Medical Monitor. Pre-medication consisting of an oral corticosteroid, such as dexamethasone (8 mg BID), for 3 days starting 1 day prior to docetaxel administration (unless contraindicated) should be considered to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions.
- 13** All AEs occurring from the time of informed consent up to and including 30 days after the last dose of study drug has been administered must be reported in detail on the AE case report form (CRF).
Note: SAE reporting is required until 30-days post the last dose of study medication.
- 14** Blood samples for PK measurements of NUC-3373 will be drawn on C1D1 and C2D1 as follows:

PK timepoint	Description
Pre-dose	Up to 30 minutes prior to administration of NUC-3373
End of infusion	Within 5 minutes before end of NUC-3373 infusion
2 hours post-infusion	±15 minutes
6 hours post-infusion	±15 minutes

The exact time each PK sample is taken must be recorded.

Note: PK sampling may be stopped with agreement from the Safety Review Committee if the Sponsor deems that sufficient samples have been collected. All study sites will be notified in writing if this decision is made.

- 15** All patients who no longer attend clinic every 8 weeks for any reason will be followed up for survival and information regarding subsequent anti-cancer medications prescribed every 12 weeks (±14 days) from the time of the last scheduled study visit until withdrawal of consent, lost to follow-up, death, or the overall end of study, whichever is earliest. A total of three attempts should be made before the patient is considered as lost to follow-up. Patients in follow-up who have not experienced disease progression should continue to attend the clinic for planned radiologic scans; however, other follow-up data can be collected remotely.

Collection of follow-up data can be performed via a telephone call with the patient where possible. Where not possible, follow-up with the patient's next of kin or physician should be performed, along with review of medical notes or national registries/databases if needed. The data collected and the follow up schedule remain as per the schedule of events. Disease progression and survival will be censored at the end of study date.

ABBREVIATIONS

5-FU	5-fluorouracil
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
C _{inf}	Concentration at the end of infusion
CL	Apparent clearance
C _{max}	Maximum plasma concentration; peak plasma concentration
CR	Complete response
CRF	Case report form
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DCR	Disease control rate
DHFR	Dihydrofolate reductase
DLT	Dose-limiting toxicity
DMA	Dimethylacetamide
DoR	Duration of response
DoSD	Duration of stable disease
DPD	Dihydropyrimidine dehydrogenase
dTMP	Deoxythymidine monophosphate
dUMP	Deoxyuridine monophosphate
dUrd	Deoxyuridine
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFR	Evaluable for response
EoT	End of treatment
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
FAS	Full analysis set
FBAL	α -fluoro- β -alanine
FUDR	Floxuridine (5-fluorodeoxyuridine)
FUDR-MP	Fluorodeoxyuridine-monophosphate
/FdUMP	
FUDR-TP	Fluorodeoxyuridine-triphosphate
/FdUTP	
FUTP	Fluorouridine triphosphate
GARFT	Glycinamide ribonucleotide formyltransferase
G-CSF	Granulocyte colony stimulating factor
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
IC ₅₀	Half-maximal inhibitory concentration

ICH-GCP	International Council for Harmonisation - Good Clinical Practice
IMP	Investigational medicinal product
IND	Investigational New Drug
INR	International normalised ratio
IV	Intravenous(ly)
LDH	Lactate dehydrogenase
LV	Leucovorin
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Regulatory Agency (UK)
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NE	Not evaluable
NSCLC	Non-small cell lung cancer
ORR	Objective Response Rate
OS	Overall survival
PD-L1	Programmed cell death ligand 1
PFS	Progression-Free Survival
PK	Pharmacokinetics
PR	Partial Response
PT	Prothrombin time
QT/QTc	QT interval / Corrected QT interval
RBC	Red blood cells
RECIST	Response Evaluation Criteria in Solid Tumours (version 1.1)
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome-related coronavirus 2
SD	Stable Disease
SOC	System Organ Class
SRC	Safety Review Committee
SRP80	Super refined polysorbate 80
$t_{1/2}$	Terminal half-life
TEAE	Treatment-emergent adverse event
TS	Thymidylate synthase
TYMP	Thymidine phosphorylase (gene)
ULN	Upper limit of normal
V_d	Volume of distribution
WBC	White blood cells
WHO DD	World Health Organisation Drug Dictionary

1 INTRODUCTION AND STUDY RATIONALE

This section presents information that is specific to the combination under study in Module 2. Refer to Section 1 of the core protocol for a general overview of NUC-3373 and the key limitations associated with 5-FU.

1.1 Non-small Cell Lung Cancer

Lung cancer is one of the most common cancers in the world and NSCLC accounts for approximately 80-85% of cases ([Ferlay *et al*, 2015](#)). NSCLC is the leading cause of cancer mortality in both men and women and patients are usually diagnosed in the later stages of the disease, resulting in a poor prognosis. Indeed, approximately 20% of patients have localised disease, 25% of patients have regional metastasis, and 55% of patients have distant metastasis at initial diagnosis ([GlobalData, 2020](#)).

NSCLC can be split into three main histological subtypes, with adenocarcinoma being the most common (50-65% of cases) followed by squamous cell carcinoma (30-40% of cases) and large cell carcinoma (5-15% of cases) ([Chen *et al*, 2014](#)). Each subtype arises in different lung cells and areas and is associated with distinct patient characteristics, for example adenocarcinomas are most common in non-smokers and young people while squamous cell carcinomas are most common in smokers and people with chronic inflammation ([GlobalData, 2020](#)). This heterogenous patient population is further segmented by genetic mutations, which are known to drive NSCLC in some populations.

In the non-squamous cell carcinoma population, mutations have been identified in immunotherapy biomarkers (PD-L1 and tumour mutational burden) and genomic biomarkers (EGFR, ALK, ROS1, BRAF, BRAF V600E, NTRK1, KRAS, MET Exon 14, RET, and HER2). By contrast, potentially actionable mutations do not appear to be prevalent in the squamous cell carcinoma population ([Chen *et al*, 2014](#)). An increased understanding of these genetic drivers of NSCLC has led to the rational design of targeted therapies, predominantly tyrosine kinase inhibitors, for patients with metastatic disease. This, in combination with the introduction of checkpoint inhibitors, has led to sustained and durable responses for patients with advanced disease. However, the majority of patients with NSCLC do not harbour actionable mutations and there remains a large unmet need.

1.2 Treatment Options for NSCLC

The treatment strategy for patients with NSCLC is determined by the stage of disease at diagnosis, histology, and the presence of driver mutations. Patients with early-stage disease (Stage I–IIIB) are generally treated with surgical resection alone or combined with chemotherapy or radiotherapy. In this early-stage disease setting, neoadjuvant or adjuvant chemotherapy and/or radiotherapy can prevent relapse and prolong survival for patients at higher risk. For patients with Stage IV disease, histology and the presence of driver mutations need to be considered when determining the best systemic or targeted therapy option ([GlobalData, 2020](#)).

In the first-line setting, patients with adenocarcinoma have a range of treatment options including chemotherapies, targeted therapies, and immunotherapies. Patients with a non-squamous histology are typically tested for driver mutations and, if an actionable mutation is identified, the relevant class of tyrosine kinase inhibitors is the standard of care treatment option. If no actionable mutation is identified, patients may be treated with a checkpoint inhibitor as monotherapy or combined with chemotherapy or targeted therapy, depending on PD-L1 status. Treatment options for patients with squamous cell carcinoma are more limited and predominantly include immunotherapy and chemotherapy ([GlobalData, 2020](#)).

Following disease progression, there is no standard of care for patients in the 2nd-line and beyond settings. Treatment is based on systemic chemoradiation therapies and patients are typically offered immunotherapy and/or chemotherapy combinations or participation in a clinical study (NCCN, 2021). However, many patients do not respond, or develop resistance, to chemotherapies and/or immunotherapies.

Chemotherapy with taxanes, docetaxel and paclitaxel, is commonly given as 2nd-/3rd-line treatment in patients who do not have driver mutations (Duma *et al*, 2019). Docetaxel and paclitaxel both have activity in advanced NSCLC, with response rates of approximately 25% for docetaxel monotherapy and 29% for paclitaxel monotherapy in patients who have progressed on prior therapy (Cersosimo, 2002). Efficacy is comparable between the two taxanes and both are associated with dose-limiting haematological toxicities (Esteban *et al*, 2003). Another option for 2nd-line treatment is the folate anti-metabolite pemetrexed, which showed similarity in survival and response rates to docetaxel but with lower toxicity (Hanna *et al*, 2004). However, despite promising activity, 2nd-line treatment typically improves survival by only 2 months compared with best supportive care (Paz-Ares *et al*, 2008). Thus, more effective and more tolerable treatment options are needed for patients with advanced NSCLC who have progressed on prior therapies.

1.3 TS inhibitors in NSCLC

Thymidylate synthase (TS) is a *de novo* pyrimidine biosynthesis enzyme that catalyses the conversion of deoxyuridine monophosphate (dUMP) to deoxythymidine monophosphate (dTMP), which is essential for DNA synthesis and cell proliferation. It is therefore targeted by chemotherapeutic drugs for the treatment of a variety of solid tumours, including NSCLC.

The anti-metabolite TS inhibitor pemetrexed is a key component of standard treatment regimens for patients with advanced non-squamous NSCLC (Tomasini *et al*, 2016). Pemetrexed inhibits cell replication and growth through the inhibition of three enzymes involved in purine and pyrimidine synthesis: TS, dihydrofolate reductase (DHFR) and glycinamide ribonucleotide formyltransferase (GARFT). Consequently, pemetrexed inhibits DNA and RNA synthesis, needed for cell growth and survival (Baldwin & Perry, 2012). The primary mechanism of action of pemetrexed is inhibition of TS, which is believed to be key to its anti-cancer activity. Therefore, many studies have assessed the impact of TS expression levels on the efficacy of pemetrexed.

In a meta-analysis of eight studies investigating the association between TS expression and clinical outcomes in patients with NSCLC treated with pemetrexed, it was found that anti-cancer response and clinical outcomes, as evaluated by PFS and OS, are generally better in patients with lower TS expression levels (Liu *et al*, 2013). In line with this, patients with squamous cell carcinoma generally respond poorly to pemetrexed compared to patients with non-squamous adenocarcinomas, which may be due to higher TS expression in squamous cell carcinoma compared to other histological subtypes (Siddiqui *et al*, 2021).

The widely used chemotherapy agent 5-FU is also a TS inhibitor; however, its use in NSCLC has been limited. It was previously believed that the use of 5-FU was inappropriate for NSCLC therapy as the lung contains high levels of the enzyme dihydropyrimidine dehydrogenase (DPD) which rapidly degrades 5-FU (Tominga *et al*, 2016). Indeed, in a study evaluating the efficacy of 5-FU as adjuvant chemotherapy in patients with lung adenocarcinoma it was shown that overall survival was inversely correlated with intra-tumoural expression of DPD, indicating that patients with low DPD expression are more sensitive to 5-FU treatment (Shintani *et al*, 2011). Importantly, for patients with low-DPD expressing tumours, those who received adjuvant 5-FU had a significantly better prognosis than those who had surgery alone, suggesting that 5-FU could be a treatment

option for some patients. Furthermore, novel fluoropyrimidines that avoid degradation by DPD, such as tegafur uracil and S-1, have shown promising activity in NSCLC (Kato *et al*, 2004; Hamada *et al*, 2005; Ichinose *et al*, 2004).

Taken together, the findings presented above support the development of novel TS inhibitors with anti-cancer activity that is independent of tumour TS levels and which avoid breakdown by DPD for the treatment of patients with NSCLC.

1.4 Module Rationale

Although much progress has been made in the treatment and personalisation of therapy options for patients with NSCLC, there remains a significant level of unmet need. The majority of patients do not harbour actionable mutations and require systemic chemotherapy options. Furthermore, many patients do not respond, or acquire resistance, to the standard of care chemotherapy regimens used in the treatment of NSCLC. Thus, novel agents that can overcome the limitations associated with conventional chemotherapies are urgently needed.

NUC-3373, a novel anti-cancer ProTide, is a pre-activated and protected form of the nucleotide analogue floxuridine (FUDR[®]), specifically designed to overcome the key shortcomings that limit the clinical utility of 5-FU and other fluoropyrimidines. Refer to Section 1 of the Core Protocol for further information on NUC-3373.

NUC-3373 is resistant to breakdown by DPD and generates substantially higher levels of the active anti-cancer metabolite fluorodeoxyuridine monophosphate (FUDR-MP or FdUMP), making it a more potent inhibitor of TS than 5-FU. NUC-3373's ability to generate high intracellular levels of FUDR-MP results in the generation of FUDR-TP (also referred to as FdUTP), which is incorporated into the DNA of cancer cells. This effect was not observed with 5-FU, indicating that NUC-3373 is not only a more potent TS inhibitor, but is also a more efficient DNA-damaging agent compared to 5-FU. Furthermore, unlike 5-FU, NUC-3373 has not been shown to generate the toxic metabolite fluorouridine triphosphate (FUTP), which is known to be misincorporated into the RNA of normal cells. This mechanism underlies many of the haematological and gastrointestinal toxicities associated with 5-FU (*e.g.*, neutropenia, diarrhea, mucositis).

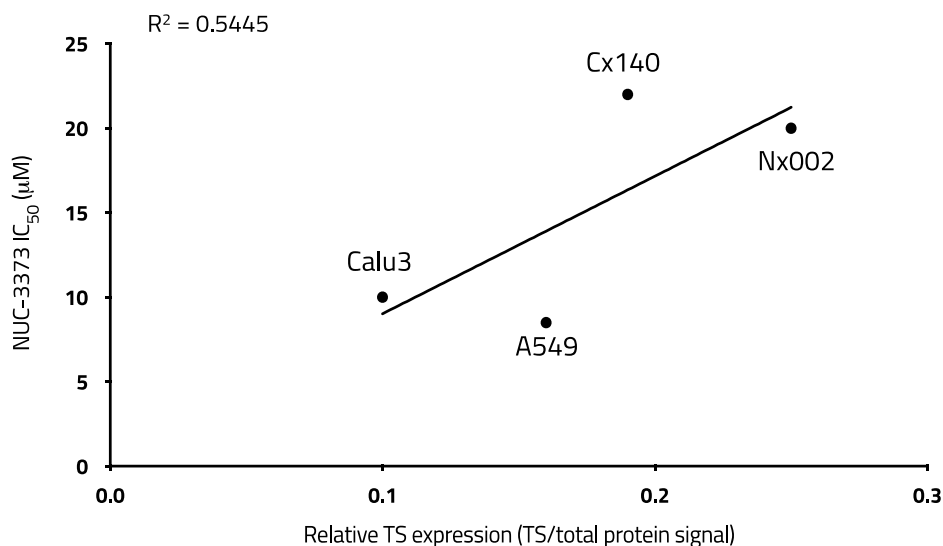
Data from nonclinical studies provide evidence that NUC-3373 is a potent TS inhibitor that could be a promising treatment option in NSCLC.

The *in vitro* cytotoxic activity of NUC-3373 and 5-FU was assessed in lung cancer cell lines using a Sulforhodamine B colorimetric assay. NUC-3373 and 5-FU were tested from 0.1 μ M to 1 mM across three timepoints (72, 120 and 168 hours). These timepoints were selected based on the doubling times of the cell lines assessed, many of which are approximately 40 hours. Across most of the cell lines tested, NUC-3373 had greater potency than 5-FU at the longer timepoints (Table 1).

Table 1 **Comparative anti-cancer activity of NUC-3373 and 5-FU in human lung cancer cell lines**

Cell line	72 hours (IC ₅₀ ; μ M)		120 hours (IC ₅₀ ; μ M)		168 hours (IC ₅₀ ; μ M)	
	NUC-3373	5-FU	NUC-3373	5-FU	NUC-3373	5-FU
NCI-H460 (large cell carcinoma)	0.3	2.6	0.02	1.3		1.2
NCI-H82 (small cell lung cancer)	1.8	12.2	0.1	4.5	0.06	4.6
NCI-H23 (adenocarcinoma)	41.9		0.1	2.2	0.1	1.5
A549 (adenocarcinoma)	15.1	2.8	0.08	0.7	0.2	0.8
NCI-H358M (adenocarcinoma)			2.9	5.9	0.2	1.9
CALU6 (adenocarcinoma)		37.3	2.4	2.6	0.6	1.5
IMR90 (fibroblast)	152.4		18.4	7.3	6.1	2.3
NCI-H292 (mucoepidermoid carcinoma)	28.5	1.9	13.6	1.2	12.2	0.7
Blank cells indicate that an IC ₅₀ could not be measured due to cell death.						

In a further set of *in vitro* studies in four human NSCLC cell lines, NUC-3373 showed cytotoxicity across all cell lines with half-maximal inhibitory concentration (IC₅₀) values in the low μ M range (Figure 1). Consistent with existing literature, the squamous cell carcinoma cells lines (Cx140 and Nx002) had higher TS expression levels than the adenocarcinoma cell lines (A549 and Calu3). The results suggest that higher TS expression is associated with lower cytotoxic activity of NUC-3373, although the correlation is weak ($R^2 = 0.5445$).

**Figure 1:** **NUC-3373 cytotoxic activity in NSCLC cells**

In addition, treatment with NUC-3373 promoted the formation of ternary complexes with TS in all four cell lines, showing that NUC-3373 is able to inhibit TS regardless of basal TS expression levels and cell histology.

In experiments comparing NUC-3373 with 5-FU or pemetrexed, NUC-3373 lead to the formation of higher levels of dUMP, quantified as a surrogate measure of TS inhibition, compared to 5-FU or pemetrexed.

The results of these *in vitro* experiments suggest that NUC-3373 may have greater anti-cancer activity than either 5-FU or pemetrexed in NSCLC and that NUC-3373 may have activity where pemetrexed has previously failed in lung cancers with squamous cell histologies.

In the clinic, NUC-3373 has shown a more favourable safety profile compared to 5-FU. This is due to differences in mechanism of action and metabolism, which results in decreased generation of toxic metabolites such as FUTP and α -fluoro- β -alanine (FBAL) and a lower incidence and reduced severity of fluoropyrimidine-related toxicities such as neutropenia, diarrhoea and hand-foot syndrome compared to 5-FU. The lack of haematopoietic toxicity observed in NUC-3373 clinical studies to date may be beneficial when combining NUC-3373 with docetaxel through minimisation of chemotherapy-induced myelosuppression, which is known to be dose-limiting for docetaxel.

Based on the nonclinical and clinical data generated to date, NUC-3373 is an attractive combination partner for docetaxel in the treatment of patients with advanced NSCLC.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Primary Objective

Phase Ib: Dose-validation phase

To determine the maximum tolerated dose (MTD) and the overall safety profile of NUC-3373 + LV in combination with docetaxel.

Phase II: Dose-expansion phase

To evaluate the preliminary anti-tumour activity of NUC-3373 + LV in combination with docetaxel.

2.2 Secondary Objectives

- To evaluate the anti-tumour activity of NUC-3373 + LV in combination with docetaxel (Phase Ib)
- To further evaluate the safety profile of NUC-3373 + LV in combination with docetaxel (Phase Ib and II)
- To evaluate the pharmacokinetics (PK) of NUC-3373 and metabolites (Phase Ib and II)

2.3 Primary Endpoints

Phase Ib: Dose-validation phase

- MTD for NUC-3373 + LV in combination with docetaxel
- Safety, as assessed by TEAEs, clinically significant laboratory changes, and changes in physical exam, vital signs and serial electrocardiograms (ECGs)

Phase II: Dose-expansion phase

- ORR, defined as the percentage of patients achieving a confirmed complete or partial response to treatment, based on RECIST v1.1 criteria

2.4 Secondary Endpoints

Efficacy (Phase Ib and 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:

- Maximum percentage change from baseline in tumour size
- ORR (Phase Ib only)
- DCR
- DoR
- DoSD
- PFS
- OS

Safety (Phase II)

- TEAEs (per CTCAE v5.0)
- Clinically significant laboratory changes (per CTCAE v5.0)
- Changes in physical exam, vital signs and serial ECGs

Pharmacokinetics (Phase Ib and II)

The PK of NUC-3373 will be assessed, including:

- C_{inf}
- C_{max}
- AUC
- $t_{1/2}$
- V_d
- CL

The analytes measured in plasma may include, but are not limited to NUC-3373, 5-FU, FBAL, dUrd.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design

This module (Module 2) describes the study design for NUC-3373 + LV in combination with docetaxel for the treatment of patients with advanced/metastatic NSCLC or pleural mesothelioma who have progressed on, or were unable to tolerate, 1 or 2 prior lines of cytotoxic chemotherapy-containing regimens.

In Phase Ib (dose-validation), approximately 6-12 evaluable patients will be enrolled in a 3+3 dose escalation design to determine the recommended dose for NUC-3373 + LV in combination with docetaxel. The exact number of patients will depend upon the number of dose escalation steps required to determine a recommended dose. Dose escalation will follow the guidelines provided in [Section 3.3.1](#).

Phase II (dose expansion) will further evaluate the combination using a Simon's two-stage design ([Simon, 1989](#)). In the first stage, 13 patients will be accrued. If there are no responses in these 13 patients, the cohort will be stopped. Otherwise, 14 additional patients will be accrued for a total of 27 patients.

3.2 Rationale for the Doses Selected

The starting dose for NUC-3373 will be 750 mg/m² in combination with LV at 400 mg/m² on Days 1 and 22 of 28-day cycles. Docetaxel will be administered at a starting dose of 55 mg/m² on Day 8 of 28-day cycles.

The proposed dose and schedule for NUC-3373 are derived predominantly from clinical data in studies NuTide:301 and NuTide:302, supported by non-clinical data.

The safety of NUC-3373 as a single agent at doses ranging from 125 to 3250 mg/m² administered on Days 1, 8, 15 and 22 of 28-day cycles has been studied in the NuTide:301 study where 2500 mg/m² weekly was identified as the MTD. NUC-3373 was well-tolerated, showing a favourable safety profile when compared to historical data for 5-FU and capecitabine.

NUC-3373 in combination with LV has been evaluated in Part 1 of the ongoing NuTide:302 study in patients with advanced colorectal cancer, where it was found that LV does not affect the safety or PK profile of NUC-3373. Based on this, it was determined that NUC-3373 should be administered in combination with the standard dose of LV (400 mg/m² weekly). It is anticipated that the addition of LV will not adversely affect the safety profile of docetaxel based on previously reported clinical studies. It has been shown that the combination of docetaxel with 5-FU and LV was well tolerated in patients with advanced gastric cancer ([Constenla et al, 2002](#)). A more recent study demonstrated the tolerability of docetaxel in combination with 5-FU, LV, oxaliplatin and trastuzumab in patients with locally advanced oesophagogastric cancer ([Hofheinz et al, 2021](#)).

In Part 2 of the NuTide:302 study, NUC-3373 has been assessed in combination with LV and either oxaliplatin (NUFOX) or irinotecan (NUFIRI). The MTD of NUC-3373 in the NUFOX regimen was determined to be 1875 mg/m² based on DLTs of Grade 3 fatigue in 2 patients and Grade 3 ALT increased/Grade 2 bilirubin increased in 1 patient. The MTD of NUC-3373 in the NUFIRI regimen was determined to be 1500 mg/m² based on DLTs of Grade 3 fatigue, Grade 3 colitis and Grade 3 ALT/ALP increased in 1 patient each.

Based on safety and tolerability data from the NuTide:301 and NuTide:302 clinical studies, and to allow room for dose escalation of both NUC-3373 and docetaxel, 750 mg/m² was selected as starting dose for NUC-3373. This dose is well below both the monotherapy MTD of 2500 mg/m²

and the combination therapy lowest MTD of 1500 mg/m², minimising the possibility of overlapping toxicities with docetaxel.

The dose and schedule for docetaxel was slightly modified from the standard regimen used for the treatment of patients with advanced NSCLC, in which docetaxel is typically administered every 3 weeks at a dose of 75 mg/m², to a 4-weekly administration schedule. This modification is for safety reasons to avoid concomitant treatment with a new agent (NUC-3373) during the post-docetaxel white blood cell nadir. Patients at the starting dose level will receive docetaxel at a dose of 55 mg/m² to assess tolerability when combined with NUC-3373 before proceeding to the standard docetaxel dose of 75 mg/m². In the absence of DLTs, dose escalation of docetaxel will occur first (at dose level 2) to ensure timely escalation of the known effective agent.

It is unknown whether there will be a potential synergistic or additive interaction between NUC-3373 and docetaxel; therefore, the selected starting doses are conservative. Based on the mechanism of action of NUC-3373, it is possible that bone marrow cell synchronisation may occur, which has the potential to exacerbate the effects of docetaxel on myelosuppression. Although the dosing schedule has been designed to minimise this by avoiding concomitant dosing, a potential interaction nevertheless cannot be completely excluded. The incidence of severe (Grade 3-4) neutropenia was found to be 65% when docetaxel monotherapy was given to patients with NSCLC at 75 mg/m² (Taxotere Prescribing Information, 2013). The docetaxel starting dose of 55 mg/m² was selected based on recommendations for dosing in the event of Grade 2-3 haematological toxicities when docetaxel is given in combination with capecitabine (Docetaxel SmPC, 2022). Thus, the starting dose is known to be efficacious and is also anticipated to minimise the risk profile of docetaxel when combined with NUC-3373. Although NUC-3373 is thought to have a different toxicity profile compared to other fluoropyrimidines, it is also thought to be a more potent TS inhibitor and so this cautious approach is warranted.

The selected starting dose for NUC-3373 is also supported by data from nonclinical and clinical studies. In lung cancer cell lines *in vitro*, NUC-3373 IC₅₀ concentrations ranged from 0.3-152.4 µM when cells were treated for 72 hours (see [Section 1.4](#)). These concentrations are much lower than drug concentrations achieved in patients receiving 750 mg/m² NUC-3373 (489 µM) in clinical studies. In PMBCs from patients treated with 750 mg/m² NUC-3373 in NuTide:301, levels of FUDR-MP (the active metabolite of NUC-3373, 5-FU, and capecitabine) were substantially higher than levels of FUDR-MP observed in PMBCs from patients treated with either 5-FU or capecitabine (Ghazaly *et al*, 2017). Therefore, synergistic or additive interactions with docetaxel, even at lower NUC-3373 doses, cannot be completely excluded.

To minimise patient exposure to sub-optimal dose levels, intra-patient dose escalation to the next dose level is permitted once that dose has been declared tolerable in at least 3 patients.

Depending on emerging safety and efficacy data, a substantial protocol amendment may be submitted to revise the docetaxel schedule to the standard 3-weekly schedule.

3.3 Study Treatment

Patients who have signed the informed consent and are eligible will be enrolled to receive treatment with NUC-3373 in combination with docetaxel. Patients may continue to receive study treatment until documentation of radiological disease progression using RECIST v1.1 or unacceptable toxicity.

Study treatment will be administered in 28-day cycles as follows:

Study drug	Infusion duration	Day 1	Day 8	Day 15	Day 22
LV	120 minutes	X		No study treatment	X
NUC-3373	120 minutes	X			X
Docetaxel*	60 minutes		X		
*Prophylactic G-CSF support is required during all cycles of treatment and should be administered in line with standard institutional practice. It is recommended that pegfilgrastim is given on Day 10 of each cycle; however, alternative agents may be discussed with the Medical Monitor.					

An initial cohort of 3 evaluable patients will receive NUC-3373 at 750 mg/m² plus LV at 400 mg/m² on Days 1 and 22 and docetaxel at 55 mg/m² on Day 8 of 28-day cycles. There will be a 28-day observation period between treatment of the first patient and treatment of subsequent patients in this first dose cohort. All patients will be monitored for dose-limiting toxicities (DLTs) during Cycle 1 and Cycle 2.

If treatment at dose level 1 is tolerable, dose escalation will proceed as described in [Table 2](#). 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.

Table 2 Anticipated dose levels to be evaluated

Dose Level*	NUC-3373 dose (mg/m ²) Days 1 and 22	LV dose (mg/m ²) Days 1 and 22	Docetaxel dose (mg/m ²) Day 8
1	750	400	55
2	750	400	75
3	1125	400	75
4	1500	400	75
*Additional dose levels may be explored if necessary.			

Once a minimum of 3 patients in a given dose cohort have completed the DLT evaluation period (Cycles 1 and 2), all available safety and PK data will be evaluated to establish the tolerability of NUC-3373 administered in combination with docetaxel. Following declaration that a dose level is tolerable, patients at the next lower dose level may be dose-escalated.

If dose level 2 is not tolerable, the docetaxel dose may be reduced to 55 mg/m² while dose escalation with NUC-3373 continues.

The dosing schedule may be adjusted based on emerging data with agreement from the Safety Review Committee (SRC).

3.3.1 Dose Escalation and Dose Modification Guidelines

Dose escalation decisions will be made according to the dose escalation guidance rules in [Table 3](#) when 3 patients in a dosing cohort have completed the DLT evaluation period or experienced a DLT prior to completing the initial DLT evaluation period cycle. To be evaluable for DLT, a patient must have received NUC-3373 + LV and docetaxel, have completed the relevant safety evaluation requirements, and must have:

- Either received 75% or more of the specified dose of each agent during the DLT evaluation period
- or*
- experienced a DLT in the evaluation period

Dose escalation decisions will occur based on review of safety information obtained during the DLT period, including AEs (regardless of causality), laboratory safety data, vital signs and ECG data. Emerging safety data for patients who continue treatment beyond Cycle 2 will also be reviewed.

Table 3 Dose escalation guidance rules

Number of Patients with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3 patients	Dose is tolerable
≥ 1 out of 3 patients	Expand cohort, if needed, to include 6 patients. • If only 1 out of 6 has DLT, dose is tolerable • If ≥ 2 have DLTs, dose is not tolerable and lower dose cohort should be explored
≥ 2 out of 3-6 patients	This dose level will be declared a non-tolerated dose and a lower dose cohort should be explored

In the case of a tolerable dose, the SRC will decide whether to explore a higher dose level or whether this dose is the recommended dose for the combination.

Patients who withdraw from study treatment prior to the end of Cycle 2 due to a DLT will not be replaced. Patients who withdraw for other reasons may be replaced.

Protocol-specific guidelines for study treatment dosage and administration are provided in detail in [Section 7.1](#) of this module. Guidelines for protocol-specific dose modifications and discontinuations of study treatment are provided in [Section 8](#) of this module.

3.3.2 Definition of Dose-Limiting Toxicity

DLT is defined as any of the following occurring during the first two treatment cycles that are not due to the protocol disease indication or to a known concurrent medical condition and are judged as clinically significant and related to study treatment.

For dose escalation, DLTs are defined as follows
Any Grade 4 AEs will be considered DLTs, with the exception of:
Neutropenia lasting <72 hours that is not associated with fever or other clinical symptoms
Lymphopenia
Electrolyte abnormalities that are not associated with clinical sequelae and are corrected with appropriate management or supplementation within 72 hours of the onset
Any Grade 3 AEs will be considered as DLTs, with the exception of:
Nausea and vomiting persisting for <2 days after optimal anti-emetic therapy
Thrombocytopaenia without significant bleeding (including platelet transfusions)
Diarrhoea persisting for <2 days after optimal anti-diarrhoeal treatment
Hypertension persisting <7 days after treatment
Infection or fever in the absence of neutropenia persisting <5 days
Rash or photosensitivity persisting <7 days after treatment
Fatigue persisting <7 days
Liver function test elevations (AST/ALT) persisting <7 days after treatment with corticosteroids
Immune-related adverse events persisting <7 days after treatment with corticosteroids
Alopecia
The following Grade 2 AEs will be adjudicated as DLTs:
Total bilirubin CTCAE v5 ≥Grade 2 with simultaneous ALT/AST CTCAE v5 ≥Grade 2
Pneumonitis persisting >7 days despite treatment with corticosteroids
Eye pain or reduction of visual acuity that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks of the initiation of topical therapy OR requires systemic treatment
Other clinically significant toxicities (cardiotoxicity, neurotoxicity) including a single event or multiple occurrences of the same event that lead to a dosing delay of >7 days in Cycle 1

4 PATIENT SELECTION

4.1 Inclusion Criteria

To be enrolled in this module, patients must meet *all* of the following criteria during the Screening period:

1. Provision of written informed consent.
2. Confirmed diagnosis of NSCLC (any histology) or pleural mesothelioma (any histology) with evidence of locally advanced/unresectable or metastatic disease.
3. Must have progressed on, or were unable to tolerate, 1 or 2 prior lines of cytotoxic chemotherapy-containing standard of care regimens for advanced/metastatic disease (not including neoadjuvant or adjuvant therapy). Additional prior lines of treatment with targeted agents or immunotherapy are allowed as long as they were not given in combination with cytotoxic chemotherapy. Prior regimens in which one drug is substituted for another due to toxicity count as 1 line of treatment. Prior treatment with docetaxel for metastatic disease is not allowed, see exclusion criterion 6.
4. Age ≥ 18 years.
5. Minimum life expectancy of ≥ 12 weeks.
6. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.
7. Measurable disease as defined by RECIST v1.1.
8. Adequate bone marrow function as defined by ANC $\geq 1.5 \times 10^9/L$, platelet count $\geq 100 \times 10^9/L$ (with no evidence of bleeding), and haemoglobin ≥ 9 g/dL.
9. Adequate liver function, as defined by serum total bilirubin $< ULN$, AST and ALT $\leq 2.5 \times ULN$ (or $\leq 5 \times ULN$ if liver metastases are present). In the event of concomitantly increased ALP values $> 2.5 \times ULN$, AST and ALT must be $< 1.5 \times ULN$.
10. Adequate renal function assessed as serum creatinine $< 1.5 \times ULN$ and glomerular filtration rate ≥ 50 mL/min (calculated by the Cockcroft-Gault method).
11. Serum albumin ≥ 3 g/dL.
12. Ability to comply with protocol requirements.
13. Female patients of child-bearing potential must have a negative pregnancy test within 7 days prior to the first study drug administration. This criterion does not apply to patients who have had a previous hysterectomy or bilateral oophorectomy. Male patients and female patients of child-bearing potential must agree to practice true abstinence or to use two forms of contraception, one of which must be highly effective. These forms of contraception must be used from the time of signing consent, throughout the treatment period, and for 6 months following the last dose of any study medication. Oral or injectable contraceptive agents cannot be the sole method of contraception.
14. Patients must have been advised to take measures to avoid or minimize exposure to UV light for the duration of study participation and for a period of 4 weeks following the last dose of study medication.

4.2 Exclusion Criteria

Patients who meet *any* of the following criteria at Screening will be excluded from the study:

1. History of hypersensitivity or current contra-indications to 5-FU, FUDR, capecitabine (refer to latest package inserts), or the components of the NUC-3373 drug product formulation (SRP80, DMA).
2. Prior history of hypersensitivity or current contra-indication to docetaxel, polysorbate 80, ethanol (anhydrous) or citric acid.
3. Residual toxicities from prior chemotherapy, immunotherapy or radiotherapy which have not regressed to Grade ≤ 1 severity (CTCAE v5.0), except for alopecia, peripheral neuropathy and ototoxicity (which are excluded if $\geq$ Grade 3).
4. Total serum bilirubin $>ULN$ and/or AST and ALT $\geq 1.5 \times ULN$ together with concomitantly increased ALP values $> 2.5 \times ULN$.
5. Chemotherapy, hormonal therapy, radiotherapy (other than a short cycle of palliative radiotherapy, *e.g.*, for bone pain*), immunotherapy, biological agents, or exposure to another investigational agent within 21 days (or four times the half-life for molecular targeted agents, whichever is shorter) of first administration of study treatment:
 - a. For nitrosoureas and mitomycin C within 6 weeks of first administration of NUC-3373
 - b. Corticosteroid treatment is allowed during screening but should be weaned to a dose of 10 mg prednisolone (or steroid equivalent) by Cycle 1 Day 1

** Palliative radiotherapy during participation in the study is permitted, but should not be concurrent with study treatment and recovery should be allowed to prevent overlapping toxicity. It should not include a target lesion.*

6. Patients who have received > 2 prior lines of cytotoxic chemotherapy-containing regimens for advanced/metastatic disease.
7. Patients who have received prior treatment with docetaxel for advanced/metastatic disease.
8. Congenital or acquired immunodeficiency (*e.g.*, serious active infection with HIV). Patients with HIV who are healthy and have a low risk of AIDS-related outcomes are eligible.
9. Symptomatic central nervous system or leptomeningeal metastases.
10. Symptomatic ascites, ascites currently requiring drainage procedures or ascites requiring drainage over the 3 months prior to date of first dose of study drug.
11. Uncontrolled concurrent cancer other than the indication under investigation. Patients with a concurrent cancer whose natural history or treatment does not have the potential to interfere with safety or efficacy assessment are eligible.
12. Presence of an active bacterial or viral infection (including SARS-CoV-2, Herpes Zoster or chicken pox), or known active hepatitis B or C.
13. Presence of any uncontrolled concurrent serious illness, medical condition or other medical history, including laboratory results, which, in the Investigator's opinion, would be likely to interfere with the patient's ability to participate in the study or with the interpretation of the results, including any of the following:

- a. Congestive heart failure (New York Heart Association Class III or Class IV)
 - b. Clinically significant coronary heart disease or myocardial infarction within 6 months of the first dose of study medication or high risk of uncontrolled arrhythmia
 - c. Unstable or poorly controlled angina pectoris
 - d. Complete left bundle branch, bifascicular block or other clinically significant abnormal ECG finding
 - e. QTc interval >470 milliseconds
 - f. History of or current risk factor for torsade de pointes (*e.g.*, heart failure, hypokalaemia, or a family history of long QT syndrome)
 - g. History of severe skin reactions
 - h. History of severe ocular disorders
 - i. Interstitial pneumonitis or pulmonary fibrosis
14. Any condition (*e.g.*, known or suspected poor compliance, psychological instability, geographical location, *etc.*) that, in the judgment of the Investigator, may affect the patient's ability to sign the informed consent and undergo study procedures.
 15. Currently pregnant, lactating or breastfeeding.
 16. Required concomitant use of drugs known to prolong QT/QTc interval.
 17. Required concomitant use of strong CYP3A4 inducers or strong CYP3A4 inhibitors. The use of strong CYP3A4 inducers within 2 weeks of first receipt of study drug or the use of strong CYP3A4 inhibitors within 1 week of first receipt of study drug is also excluded.
 18. Use of live attenuated vaccines against infectious diseases (*e.g.*, measles mumps rubella [MMR combined vaccines], Rotavirus, Chickenpox, yellow fever) within 4 weeks of initiation of study treatment.
 19. Known DPD or TYMP mutations associated with toxicity to fluoropyrimidines.
 20. Full-dose anti-coagulation treatment is prohibited. Use of warfarin and other types of long-acting anti-coagulants (such as phenprocoumon and anti-Xa inhibitors with a half-life of >12 hours) is prohibited within 4 weeks of the first dose of study treatment. Patients requiring low dose anti-coagulant treatment should switch to low molecular weight heparin or anti-Xa inhibitors with a half-life of ≤12 hours.

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Screening Assessments

Screening assessments of consented patients will comprise the following:

- Provision of written informed consent
- Eligibility confirmation
- Recording of demographic data
- Assessment of medical and surgical history
- Recording of concomitant medication
- Routine physical examination, including vital signs. Full physical examination includes ears, eyes, nose, head, throat, neck, lungs, heart, abdomen, extremities, skin, musculoskeletal, nervous system, and lymph nodes. Vital signs include measurement of pulse rate, respiratory rate, blood pressure and temperature, after the patient has been seated or in the supine position for 5 minutes
- Urinalysis: pH, specific gravity, ketones, leukocytes, protein, glucose, bilirubin, urobilirubin and occult blood. Dipstick testing is acceptable
- ECOG performance status
- Height and weight
- Baseline assessment of symptoms
- 12-lead ECG
 - The 12-lead ECGs should be reviewed by the Investigator or a qualified designee for safety and quality
 - The QTc interval should be calculated using the Fridericia formula. Management of QT/QTc prolongation should be performed in accordance with institutional standard of care at the discretion of the treating physician
 - Digital and certified paper copies should be retained at site and stored as part of the study documents in the event they need to be used in a future analysis
- Blood samples drawn for:
 - Pregnancy testing: For women of childbearing potential serum pregnancy must be performed within 7 days of first dose
 - Haematology: white blood cell (WBC) count, differential WBC count, red blood cell count (RBC), haemoglobin, haematocrit and platelets
 - Chemistry: sodium, potassium, magnesium, urea, creatinine, glucose, phosphate, total protein, albumin, adjusted calcium, total bilirubin, direct bilirubin, indirect bilirubin, bicarbonate, chloride, uric acid, alkaline phosphatase (ALP), AST, ALT and lactate dehydrogenase (LDH)
 - Coagulation parameters: prothrombin time/international normalised ratio (PT/INR) and activated partial thromboplastin time (aPTT)

- Tumour imaging (CT or MRI) – performed within 28 days of C1D1. A recent previously obtained image may be used if obtained within 28 days of C1D1 and images collected meet protocol requirements.
- Advise the patient to take measures to avoid or minimise exposure to UV light for the duration of study participation and for a period of 4 weeks following the last dose of study medication
- Patient registration

5.2 Evaluations to be Performed During the Study

During the treatment period, the assessments detailed in the sections below and summarised in the [Summary Schedule of Events](#) will be performed.

Collection of prior scan reports for assessment of previous tumour measurements can be performed any time during patient participation in the study or during follow-up. This will allow understanding of the trajectory of tumour growth prior to the patient entering this study.

5.2.1 Each Cycle, Day 1

All procedures to be completed prior to dosing except applicable PK samples:

- Recording of new or changes to concomitant medication.
- Physical examination
 - Full physical examination (including neurological examination) to be performed on C1D1 and C2D1 only in Phase Ib and on C1D1 only in Phase II. Full physical examination includes ears, eyes, nose, head, throat, neck, lungs, heart, abdomen, extremities, skin, musculoskeletal, nervous system, and lymph nodes.
 - Directed physical examination (directed by clinical signs and symptoms, including neurological examination), only if clinically indicated, to be performed from Cycle 3 onwards in Phase Ib and from Cycle 2 onwards in Phase II
- Urinalysis: pH, specific gravity, ketones, leukocytes, protein, glucose, bilirubin, urobilirubin and occult blood. Dipstick testing is acceptable
- ECOG performance status
- Vital signs, including measurement of pulse rate, respiratory rate, blood pressure and temperature, after the patient has been seated or in the supine position for 5 minutes
- Weight
- **Pre-dose ECGs:** 12-lead ECGs should be performed prior to infusion of all IMPs. *Note: on C1D1 the 12-lead ECG should also be performed post-infusion of NUC-3373 (Section 5.2.2)*
 - The ECGs should be reviewed by the Investigator or a qualified designee for safety and quality
 - The QTc interval should be calculated using the Fridericia formula. Management of QT/QTc prolongation should be performed in accordance with institutional standard of care at the discretion of the treating physician

- Digital and certified paper copies should be retained at site and stored as part of the study documents in the event they need to be used in a future analysis
- Urine pregnancy test for women of child-bearing potential. If any urine test result is positive, patient dosing will be postponed until the result is confirmed by a serum pregnancy test. Any patient with a positive serum test will not be allowed to receive any study treatment
- Blood samples drawn for:
 - Haematology: WBC count, differential WBC count, RBC, haemoglobin, haematocrit and platelets
 - Chemistry: sodium, potassium, magnesium, urea, creatinine, glucose, bicarbonate, chloride, uric acid, phosphate, total protein, albumin, adjusted calcium, total bilirubin, direct bilirubin, indirect bilirubin, ALP, AST, ALT and LDH
 - Coagulation parameters: PT/INR and aPTT
- IV administration of study drug:
 - NUC-3373 + LV
- AE recording and causality assessment

5.2.2 Cycle 1 ONLY

- **Post-dose ECGs:** In addition to the pre-dose ECGs performed on Day 1 of each cycle, 12-lead ECGs should also be performed post-infusion of NUC-3373 on C1D1 only
 - The ECGs should be reviewed by the Investigator or a qualified designee for safety and quality
 - The QTc interval should be calculated using the Fridericia formula. Management of QT/QTc prolongation should be performed in accordance with institutional standard of care at the discretion of the treating physician
 - Digital and certified paper copies should be retained at site and stored as part of the study documents in the event they need to be used in a future analysis

5.2.3 Cycles 1 & 2 ONLY

- Blood samples for PK measurements on C1D1 and C2D1 only – Refer to [Section 6.1](#) for more details

5.2.4 Each cycle, Day 8

If a patient stops docetaxel treatment for any reason, the Day 8 visit may be performed by telephone call to collect information on AEs and concomitant medications.

All procedures to be completed prior to dosing:

- Recording of new or changes to concomitant medications
- Vital signs, including measurement of pulse rate, respiratory rate, blood pressure and temperature, after the patient has been seated or in the supine position for 5 minutes

- Blood samples drawn for:
 - Haematology: WBC count, differential WBC count, RBC, haemoglobin, haematocrit and platelets
 - Chemistry: sodium, potassium, magnesium, urea, creatinine, glucose, bicarbonate, chloride, uric acid, phosphate, total protein, albumin, adjusted calcium, total bilirubin, direct bilirubin, indirect bilirubin, ALP, AST, ALT and LDH
 - Coagulation parameters: PT/INR and aPTT
- IV administration of study drug:
 - Docetaxel
- AE recording and causality assessment

5.2.5 Each cycle, Day 15

Note there is no study treatment dosing on Day 15.

- Recording of new or changes to concomitant medications
- Vital signs, including measurement of pulse rate, respiratory rate, blood pressure and temperature, after the patient has been seated or in the supine position for 5 minutes
- Blood samples drawn for:
 - Haematology: WBC count, differential WBC count, RBC, haemoglobin, haematocrit and platelets
 - Chemistry: sodium, potassium, magnesium, urea, creatinine, glucose, bicarbonate, chloride, uric acid, phosphate, total protein, albumin, adjusted calcium, total bilirubin, direct bilirubin, indirect bilirubin, ALP, AST, ALT and LDH
 - Coagulation parameters: PT/INR and aPTT
- AE recording and causality assessment

5.2.6 Each cycle, Day 22

All procedures to be completed prior to dosing with study drug:

- Recording of new or changes to concomitant medications
- Vital signs, including measurement of pulse rate, respiratory rate, blood pressure and temperature, after the patient has been seated or in the supine position for 5 minutes
- Blood samples drawn for:
 - Haematology: WBC count, differential WBC count, RBC, haemoglobin, haematocrit and platelets
 - Chemistry: sodium, potassium, magnesium, urea, creatinine, glucose, bicarbonate, chloride, uric acid, phosphate, total protein, albumin, adjusted calcium, total bilirubin, direct bilirubin, indirect bilirubin, ALP, AST, ALT and LDH
 - Coagulation parameters: PT/INR and aPTT

- IV administration of study drug:
 - NUC-3373 + LV
- AE recording and causality assessment

5.2.7 Every 8 weeks (± 7 days) from Cycle 1 Day 1 until disease progression, initiation of a new treatment or death

- Tumour imaging (CT, or MRI)
 - CRs and PRs must be confirmed by repeated measurement. The confirmatory scans should be performed at least 28 days and not more than 42 days after initial assessment of response
 - If a patient is found to have a response at the confirmatory scan which has improved from PR to CR, then the improved response must also be confirmed within a further 28- to 42-day window
 - Additional tests may be requested at the Investigator's discretion. The same modality should be used throughout

5.2.8 End of Treatment Visit

The assessments to be performed on discontinuation due to radiological disease progression or early treatment discontinuation for other reasons (*e.g.*, withdrawal of consent) are summarised below. The End of Treatment (EoT) visit should occur within a minimum of 30 days to a maximum of 37 days following the last administration of any study medication. During the EoT visit, the following items will be assessed:

- Recording of new or changes to concomitant medication
- Full physical examination, including vital signs. Full physical examination includes ears, eyes, nose, head, throat, neck, lungs, heart, abdomen, extremities, skin, musculoskeletal, nervous system, and lymph nodes. Vital signs include measurement of pulse rate, respiratory rate, blood pressure and temperature, after the patient has been seated or in the supine position for 5 minutes, and temperature
- Urinalysis: pH, specific gravity, ketones, leukocytes, protein, glucose, bilirubin, urobilirubin and occult blood. Dipstick testing is acceptable
- ECOG performance status
- Weight
- 12-lead ECG
 - The 12-lead ECGs should be reviewed by the Investigator or a qualified designee for safety and quality
 - The QTc interval should be calculated using the Fridericia formula. Management of QT/QTc prolongation should be performed in accordance with institutional standard of care at the discretion of the treating physician

- Digital and certified paper copies should be retained at site and stored as part of the study documents in the event they need to be used in a future analysis
- Blood samples drawn for:
 - Pregnancy testing for women of child-bearing potential
 - Haematology: WBC count, differential WBC count, RBC, haemoglobin, haematocrit and platelets
 - Chemistry: sodium, potassium, magnesium, urea, creatinine, glucose, bicarbonate, chloride, uric acid, phosphate, total protein, albumin, adjusted calcium, total bilirubin, direct bilirubin, indirect bilirubin, ALP, AST, ALT and LDH
 - Coagulation parameters: PT/INR and aPTT
- AE recording and causality assessment

5.2.9 Follow-Up

Patients who stop treatment with no evidence of radiological disease progression as defined by RECIST v1.1 criteria will continue to receive scans at regular intervals (every 8 weeks [± 7 days] from C1D1) until disease progression, initiation of a new treatment, or death (whichever comes first) in order to determine duration of overall response and PFS.

All patients who no longer attend clinic every 8 weeks for any reason will be followed up for survival and information regarding subsequent anti-cancer medications prescribed every 12 weeks (± 14 days) from the time of the last scheduled study visit until withdrawal of consent, lost to follow-up, death, or the overall end of study, whichever is earliest. A total of three attempts should be made before the patient is considered as lost to follow-up. Patients in follow-up who have not experienced disease progression should continue to attend the clinic for planned radiologic scans; however, other follow-up data can be collected remotely.

5.2.10 Patient Evaluability and Replacement

All patients who receive any study treatment are considered evaluable for safety analysis.

All patients with measurable disease who undergo at least 2 cycles of treatment, receive at least 75% of planned treatment in that 2-cycle period, and undergo a post-treatment objective disease assessment, will be considered evaluable for response assessment.

6 SAMPLES FOR LABORATORY ANALYSIS

6.1 Pharmacokinetics

The PK schedule is designed to explore the relationship between the pharmacokinetics of NUC-3373 and safety and clinical activity.

Blood samples will be collected at four timepoints on C1D1 and C2D1.

The analytes measured in plasma may include, but are not limited to:

- NUC-3373, 5-FU, FBAL, dUrd

Standard PK parameters for each compound of interest will then be derived from the measured plasma concentrations. The PK samples will be processed and analysed at a central laboratory. Please refer to the PK and Translational Laboratory Manual for details regarding PK sample collection, processing and shipping.

Note: PK sampling may be stopped with agreement from the SRC if the Sponsor deems that sufficient samples have been collected. All study sites will be notified in writing if this decision is made.

The PK sampling schedule is summarised in Table 4.

Table 4 PK sampling schedule

PK timepoint	Description
Pre-dose	Up to 30 minutes prior to administration of NUC-3373
End of infusion	Within 5 minutes before end of NUC-3373 infusion
2 hours post-infusion	±15 minutes
6 hours post-infusion	±15 minutes

The exact time that each PK sample is taken must be recorded.

7 INVESTIGATIONAL MEDICINAL PRODUCTS

7.1 Treatment Administration

7.1.1 Dose escalation Phase

The starting dose for NUC-3373 will be 750 mg/m² and the starting dose for docetaxel will be 55 mg/m². An initial cohort of 3 evaluable patients will receive 750 mg/m² NUC-3373 in combination with 400 mg/m² LV on Days 1 and 22, along with docetaxel at a dose of 55 mg/m² on Day 8, of 28-day cycles. There will be a 28-day observation period between treatment of the first patient and treatment of subsequent patients in this first dose cohort. All patients will be monitored for DLTs during Cycle 1 and Cycle 2.

Pre-medication consisting of an oral corticosteroid, such as dexamethasone (8 mg BID), for 3 days starting 1 day prior to docetaxel administration (unless contraindicated) should be considered to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions.

In the initial dose cohort, study treatment will be administered in 28-day cycles as follows:

1. LV 400 mg/m² IV (or equivalent levo-leucovorin [200 mg/m²]) over 120 minutes prior to each NUC-3373 infusion on Days 1 and 22
2. NUC-3373 IV over 120 minutes at an initial dose of 750 mg/m² on Days 1 and 22
3. Docetaxel IV over 60 minutes at an initial dose of 55 mg/m² on Day 8*

*Prophylactic G-CSF support is required during all cycles of treatment and should be administered in line with standard institutional practice. It is recommended that pegfilgrastim is given on Day 10 of each cycle; however, alternative agents may be discussed with the Medical Monitor.

Starting doses for subsequent cohorts will follow the dose escalation schedule described in [Table 2](#).

The dosing schedule may be adjusted based on emerging data with agreement from the SRC.

Please refer to the current Pharmacy Manual for further information on NUC-3373 preparation and administration.

7.1.2 Dose-expansion Phase

Following completion of the dose escalation phase, expansion cohorts may be initiated at the selected dose level.

7.2 Interaction with Other Drugs

Patients receiving NUC-3373 should be carefully managed for potential drug interactions according to local practice. Refer to [Section 9](#) for information regarding the use of prohibited therapies and therapies to be used with caution.

Interactions between docetaxel and any concomitant medications should be checked with the respective package inserts in accordance with local practice. Local practice and guidelines should be followed for the management of any potential docetaxel/concomitant medication interactions.

8 MANAGEMENT OF TOXICITY

Adverse events may be managed by dose delays and/or dose reductions according to the clinical situation.

If a NUC-3373 and/or docetaxel dose reduction is indicated, the dose should initially be reduced to the next lower dose level for the drug, as shown in [Table 5](#).

Table 5 Dose reduction guidelines

NUC-3373 dose (mg/m ²) Days 1 and 22	LV dose (mg/m ²) Days 1 and 22	Docetaxel dose (mg/m ²) Day 8
1500	400	75
1125	400	55
750	400	45
500	400	37.5

Dose reductions may be temporary, in which case the next cycle can revert to the starting dose of the previous cycle, or permanent, which would apply to all subsequent cycles. Over the whole dosing period, each patient may have a maximum of 2 permanent dose reductions, after which treatment will be discontinued and the patient will be removed from study.

Treatment between cycles can be delayed for up to 28 days for patients to meet the re-treatment criteria before starting their next cycle. Patients who do not meet these requirements after this additional time will not be allowed to receive further cycles of treatment and will be withdrawn from the study unless the patient is receiving clinical benefit in the opinion of the Investigator.

In patients receiving clinical benefit, AEs attributed to docetaxel may be managed by dose adjustment, delays or discontinuation of docetaxel in accordance with standard clinical practice. Treatment with NUC-3373 must be continued for the patient to remain on treatment for the purposes of this protocol.

8.1 Criteria for Continuation of Treatment

Patients must meet all of the following criteria prior to receiving a dose of study treatment:

- ANC
 - $\geq 1.5 \times 10^9/\text{L}$ for full treatment dose (except Day 22 [NUC-3373 + LV only] of each cycle, which may be given with ANC $\geq 1.0 \times 10^9/\text{L}$ after approval from the Medical Monitor)
 - $\geq 1.0 \times 10^9/\text{L}$ for reduced treatment dose (see Table 6)
- Platelet count $\geq 100 \times 10^9/\text{L}$ (except Day 22 [NUC-3373 + LV only] of each cycle, which may be given with platelets $\geq 70 \times 10^9/\text{L}$ after approval from the Medical Monitor)
- No evidence of disease progression (based on radiographic assessment)
- Recovery from all clinically significant toxicities to $\leq$ Grade 2 or to baseline grade present at study entry

If a patient fails to meet any of these criteria, administration of study drug should be held until all re-treatment criteria are met. If a DLT occurs during a cycle, doses of study drug will be withheld

for the remainder of the cycle and subsequent cycles will be administered at the previously tested next lower dose level. The study drugs can be withheld for a maximum of 28 days; if the delay is >28 days, the patient must be withdrawn from treatment, unless the patient is receiving clinical benefit.

8.2 Dose Modifications

Treatment between cycles can be delayed for up to 28 days for patients to meet the re-treatment criteria before starting their next cycle. Patients who fail to meet these requirements after this additional time will not be allowed to receive further cycles of therapy within the study unless they are receiving clinical benefit in the opinion of the Investigator. If a patient experiences multiple toxicities, dose adjustments will be based on the most severe toxicity. A patient who experiences a toxicity meeting the definition of DLT (during any cycle) but whose toxicity recovers within 28 days may be dose reduced to the next lower dose level. If a patient experiences a sub-DLT toxicity, they may be dose reduced in line with [Table 6](#).

Any patient who experiences one or more recurrent, clinically significant toxicity after the initial dose reduction may have one further dose reduction. Patients who continue to experience clinically significant toxicity despite two dose reductions will be discontinued from study treatment. A patient receiving clinical benefit will not require discontinuation and treatment guidelines for such patient will be decided in discussion with the Investigator, Medical Monitor and SRC.

General guidance for dose modifications of NUC-3373 and/or docetaxel in response to common toxicities is provided in [Table 6](#).

If the planned dose(s) on a particular visit cannot be administered during that planned visit for any reason and needs to be delayed, the drug(s) may subsequently be administered within the next 24 hours. If the delay needs to be longer than 24 hours, then the planned dose(s) should be skipped and treatment should be delayed until the next planned dose.

Table 6 Dose modifications for Cycle 3 onwards and for non-DLT toxicities within Cycles 1 and 2

Toxicity Grade	During a cycle of therapy		At the start of subsequent cycles of therapy ^a	
	NUC-3373	Docetaxel	NUC-3373	Docetaxel
Neutropenia				
Grade 1 (LLN – 1500/mm ³)	Maintain dose level	Maintain dose level	Maintain dose level	Maintain dose level
Grade 2 (<1500 – 1000/mm ³)	Reduce by 1 dose level for the next administration	Omit dose until resolved to ≤Grade 1 Then resume at previous dose level	1 episode: Maintain starting dose used in previous cycle ≥2 episodes: Maintain reduced dose level	Maintain starting dose used in previous cycle
Grade 3 (<1000 – 500/mm ³)	Omit dose until resolved to ≤Grade 1 Then resume at previous dose level	Omit dose until resolved to ≤Grade 1 Then reduce by 1 dose level	Maintain starting dose used in previous cycle	Maintain reduced dose level
Grade 4 (<500/mm ³)	Omit dose until resolved to ≤Grade 1 Then reduce by 1 dose level	Omit dose until resolved to ≤Grade 1 Then reduce by 1 dose level	Maintain reduced dose level	Maintain reduced dose level
Neutropenic fever				
All	Omit dose until resolved (no fever and ≤Grade 1 neutropenia) Then resume at previous dose level	Omit dose until resolved to ≤Grade 1 Then reduce by 1 dose level	Maintain dose level	Maintain reduced dose level
Thrombocytopaenia				
Grade 1	Maintain dose level	Maintain dose level	Maintain dose level	Maintain dose level
Grade 2	Reduce by 1 dose level for the next administration	Omit dose until resolved to a platelet count of ≥100×10 ⁹ /L Then resume at previous dose level	1 episode: Maintain starting dose used in previous cycle ≥2 episodes: Maintain reduced dose level	Maintain starting dose used in previous cycle

Toxicity Grade	During a cycle of therapy		At the start of subsequent cycles of therapy ^a	
	NUC-3373	Docetaxel	NUC-3373	Docetaxel
Grade 3	Omit dose until resolved to ≤Grade 1 Then resume at previous dose level	Omit dose until resolved to a platelet count of ≥100×10 ⁹ /L Then resume at previous dose level	Maintain starting dose used in previous cycle	Maintain starting dose used in previous cycle
Grade 4	Omit dose until resolved to ≤Grade 1 Then reduce by 1 dose level	Omit dose until resolved to a platelet count of ≥100×10 ⁹ /L Then reduce by 1 dose level	Maintain reduced dose level	Maintain reduced dose level
Other haematologic toxicities				
All	Dose modifications for leukopaenia or lymphopenia during a cycle of therapy and at the start of subsequent cycles of therapy are not required.			
Diarrhoea				
Grade 1	Continue dosing, depending on clinical judgement	Continue dosing, depending on clinical judgement	Maintain dose level	Maintain dose level
Grade 2	Omit dose until resolved to baseline Then reduce by 1 dose level	Continue dosing, depending on clinical judgement	1 episode: Maintain starting dose used in previous cycle ≥2 episodes: Maintain reduced dose level	Maintain dose level
Grade 3	Omit dose until resolved to baseline Then reduce by 1 dose level	Continue dosing, depending on clinical judgement	Maintain reduced dose level	Maintain dose level
Grade 4	Omit dose until resolved to baseline Then reduce by 2 dose levels	Omit dose until resolved to baseline Then reduce by 1 dose level	Maintain reduced dose level	Maintain reduced dose level
Hepatotoxicity				
AST/ALT 2.5 - 5 x ULN & ALP ≥2.5 x ULN OR	Omit dose until resolved to baseline Then reduce by 1 dose level	Omit dose until resolved to baseline Then reduce by 1 dose level	Maintain reduced dose level	Maintain reduced dose level

Toxicity Grade	During a cycle of therapy		At the start of subsequent cycles of therapy ^a	
	NUC-3373	Docetaxel	NUC-3373	Docetaxel
AST/ALT 1.5 - 5 x ULN & ALP 2.5 - 5 x ULN				
AST/ALT >5 x ULN AND/OR ALP >5 x ULN	Discontinue	Discontinue	Discontinue	Discontinue
Bilirubin Grade 1-2	Omit dose until resolved to baseline Then reduce by 1 dose level	Omit dose until resolved to baseline Then reduce by 1 dose level	Maintain reduced dose level	Maintain reduced dose level
Bilirubin Grade ≥3	Discontinue	Discontinue	Discontinue	Discontinue
Cardiotoxicity				
All	In case of severe cardiotoxicity, discontinue NUC-3373 treatment.			
Other non-haematologic toxicities ^b				
Grade 1	Maintain dose level	Maintain dose level	Maintain dose level	Maintain dose level
Grade 2	Reduce by 1 dose level for the next administration	Omit dose until resolved to ≤Grade 1 Then reduce by 1 dose level	1 episode: Maintain starting dose used in previous cycle ≥2 episodes: Maintain reduced dose level	Maintain starting dose used in previous cycle
Grade 3 ^c	Omit dose until resolved to ≤Grade 2 Then reduce by 1 dose level	Omit dose until resolved to ≤Grade 1 or baseline Then reduce by 1 dose level	Maintain reduced dose level	Maintain reduced dose level
Grade 4	Omit dose until resolved to ≤Grade 2 Then reduce by 2 dose levels	Omit dose until resolved to ≤Grade 1 or baseline Then reduce by 1 dose level	Maintain reduced dose level	Maintain reduced dose level

Toxicity Grade	During a cycle of therapy		At the start of subsequent cycles of therapy ^a	
	NUC-3373	Docetaxel	NUC-3373	Docetaxel
^a Relative to the starting dose used in the previous cycle ^b Excludes alopecia, anorexia, asthenia ^c Grade 3 peripheral neuropathy requires discontinuation of docetaxel				

Management of docetaxel toxicities

Pre-medication consisting of an oral corticosteroid, such as dexamethasone (8 mg BID), for 3 days starting 1 day prior to docetaxel administration (unless contraindicated) should be considered to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions.

The most commonly-reported adverse reactions associated with docetaxel alone are neutropenia (which is reversible and not cumulative; the median to nadir is 7 days and the median duration of severe neutropenia [$<0.5 \times 10^9/L$] is 7 days), anaemia, alopecia, nausea, vomiting, stomatitis, diarrhoea and asthenia. The severity of adverse events may be increased when docetaxel is given in combination with other chemotherapeutic agents.

Patients receiving docetaxel should be closely monitored for the following adverse reactions.

Gastrointestinal complications

Caution is recommended for patients with neutropenia, particularly at risk for developing gastrointestinal complications. Although the majority of cases occur during the first or second cycle of docetaxel-containing regimens, enterocolitis could develop at any time, and could lead to death as early as the first day of onset.

Hypersensitivity reactions

Close monitoring is recommended, especially during the first and second infusions. Hypersensitivity reactions may occur within a few minutes following the initiation of infusion, thus facilities for the treatment of hypotension and bronchospasm should be available.

If hypersensitivity reactions occur:

- Minor symptoms (*e.g.*, flushing or localised cutaneous reactions) do not require interruption of docetaxel.
- Severe reactions (*e.g.*, severe hypotension, bronchospasm or generalised rash/erythema) require immediate discontinuation of docetaxel and appropriate therapy.

Patients who have developed severe hypersensitivity reactions should not be re-challenged with docetaxel. Patients who have previously experienced a hypersensitivity reaction to paclitaxel may be at risk to develop hypersensitivity reactions to docetaxel, including more severe hypersensitivity reactions.

Cutaneous toxicity

Localised skin erythema of the extremities (palms of the hands and soles of the feet) with oedema followed by desquamation has been observed. Severe symptoms such as eruptions followed by desquamation have been reported to lead to interruption or discontinuation of docetaxel treatment. Severe cutaneous adverse reactions such as Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis and Acute Generalized Exanthematous Pustulosis have been reported with docetaxel treatment.

Patients should be informed about the signs and symptoms of serious skin manifestations and closely monitored. If signs and symptoms suggestive of these reactions appear discontinuation of docetaxel should be considered.

Fluid retention

Patients with severe fluid retention such as pleural effusion, pericardial effusion and ascites should be monitored closely.

Pulmonary toxicity

Acute respiratory distress syndrome, interstitial pneumonia/pneumonitis, interstitial lung disease, pulmonary fibrosis and respiratory failure have been reported and may be associated with fatal outcome. Cases of radiation pneumonitis have been reported in patients receiving concomitant radiotherapy.

If new or worsening pulmonary symptoms develop:

- Patients should be closely monitored, promptly investigated, and appropriately treated.
- Interruption of all study treatment is recommended until diagnosis is available.
- Early use of supportive care measures may help improve the condition.
- The benefit of resuming study treatment must be carefully evaluated.

Cardiac toxicity

Heart failure has been observed in patients receiving docetaxel in combination with trastuzumab, particularly following anthracycline (doxorubicin or epirubicin)- containing chemotherapy. This may be moderate to severe and has been associated with death.

Ventricular arrhythmia including ventricular tachycardia (sometimes fatal) has been reported in patients treated with docetaxel in combination regimens including doxorubicin, 5-fluorouracil and/or cyclophosphamide.

Ophthalmologic toxicity

Cystoid macular oedema (CMO) has been reported in patients treated with docetaxel. Patients with impaired vision should undergo a prompt and complete ophthalmologic examination. In case CMO is diagnosed, all study treatment should be discontinued and appropriate treatment initiated.

Second primary malignancies

Second primary malignancies (including acute myeloid leukaemia, myelodysplastic syndrome and non-Hodgkin lymphoma) have been reported when docetaxel is given in combination with anti-cancer treatments known to be associated with second primary malignancies. They may occur several months or years after docetaxel-containing therapy.

Genotoxicity

In non-clinical studies, docetaxel has genotoxic effects and may alter male fertility. Therefore, men being treated with docetaxel are advised not to father a child during and up to 6 months after treatment and to seek advice on conservation of sperm prior to treatment.

Excipients

Docetaxel contains 50 vol % ethanol (alcohol), *i.e.*, up to 3.16 g (4 mL) ethanol anhydrous per vial of 8 mL fill volume, equivalent to 80 mL beer or 33 mL wine per 8 mL vial. Harmful for those suffering from alcoholism. To be taken into account in high-risk groups such as patients with liver disease, or epilepsy. Patients should be warned of the potential impact of the amount of alcohol

and the side effects of docetaxel on the ability to drive or use machines, and be advised not to drive or use machines if they experience these side effects during treatment.

Overdose

There is no known antidote for docetaxel overdose. In case of overdose, the patient should be kept in a specialised unit and vital functions closely monitored. Exacerbation of adverse events may be expected. The primary anticipated complications of overdose consist of bone marrow suppression, peripheral neurotoxicity and mucositis. Patients should receive therapeutic G-CSF as soon as possible after discovery of overdose. Other appropriate symptomatic measures should be taken, as needed.

9 OTHER TREATMENTS (NON-IMP)

9.1 Prohibited Therapies

Except as included in the specific modules and dosing regimens of this study, use of the following therapies is prohibited (at any dose and at any time) during the study:

- Other cytotoxic chemotherapy
- Radiotherapy, excluding a short cycle of palliative radiotherapy
- Immunotherapy, including immunosuppressive therapy
- Radioimmunotherapy
- Hormone therapy (other than contraceptives, hormone-replacement therapy, anti-hormonal treatment for patients with prostate cancer, or megestrol acetate)
- Other biologic agents intended for the treatment of cancer under investigation (other than haematopoietic growth factors)
- Any therapies intended for the treatment of cancer under investigation, whether approved by local regulatory authorities or investigational, with the exception of treatments for patients with a concurrent well-controlled cancer (as per Exclusion Criterion 11)
- Drugs that are known to prolong QTc interval (refer to Appendix 4 of the core protocol)
- Strong inducers of CYP3A4, including but not limited to phenytoin, phenobarbital, carbamazepine, rifampin, rifabutin or St. John's wort
- Strong inhibitors of CYP3A4, including but not limited to ketoconazole, clarithromycin, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, ritonavir, saquinavir, or atazanavir
- Live vaccines, including live attenuated vaccines (must also be avoided for six weeks after last dose of study medication)
- Diuretics and laxatives should be avoided in patients experiencing treatment-related diarrhoea and cholinergic reactions
- Warfarin and other long-acting anticoagulants with a half-life of >12 hours (prohibited from 4 weeks prior to the first dose of study treatment until after the last dose of study treatment)

9.2 Therapies to be Used with Caution

For patients in all modules of the study, warfarin and other types of long-acting anti-coagulants (such as phenprocoumon and anti-Xa inhibitors with a half-life of >12 hours) are prohibited from 4 weeks prior to the first dose of study treatment until after the last dose of study treatment. Patients requiring low dose anti-coagulant treatment should switch to low molecular weight heparin or anti-Xa inhibitors with a half-life of ≤12 hours.

In vitro studies have shown the potential for NUC-3373 drug-drug interaction with concomitant medications that are metabolised by CYP3A4 and CYP2C8. The clinical impact of these *in vitro* observations is not known and the use of concomitant medications that are cleared by these CYP enzymes is permitted with caution in patients receiving NUC-3373.

In vitro studies have shown that the metabolism of docetaxel may be modified by the concomitant administration of compounds which induce, inhibit or are metabolised by (and thus may inhibit the enzyme competitively) Cytochrome P450-3A, such as cyclosporine, ketoconazole and erythromycin. As a result, caution should be exercised when treating patients with these medicinal products as concomitant therapy since there is the potential for a significant interaction.

10 TUMOUR RESPONSE ASSESSMENTS

Patients must have at least one lesion that can be accurately assessed at baseline by CT or MRI and which is suitable for repeated assessment in order to be eligible for this study. All known or suspected disease sites must be assessed at baseline by either CT or MRI scan as appropriate. Additional anatomical areas should be assessed by CT or MRI in case of suspicion of presence of metastases based on signs, symptoms, biochemical results and/or as standard of care imaging of patients (*i.e.*, non-study related). The same measurement method used at baseline must be used to follow lesions throughout the study. Disease status must be assessed according to RECIST v1.1 criteria, with target and non-target lesions identified, measured and followed throughout the study (Appendix 1 of the core protocol). Biopsied lesions should not be designated as target lesions for the purposes of RECIST v1.1 and a target lesion should not be biopsied during the study unless medically necessary.

Whenever possible, the same qualified physician will interpret results to reduce variability. Radiographic images will be maintained at the study centre and Investigator's assessments will be filed in the patient's source documents.

Tumour measurements and disease response assessments are to be performed every 8 weeks (± 7 days) from Cycle 1 Day 1. If the patient stops study treatment for reasons other than confirmed progressive disease per RECIST v1.1, tumour measurements and disease response assessments should continue every 8 weeks (± 7 days) from Cycle 1 Day 1 until progressive disease is confirmed.

Tumour measurements and disease response assessments should be performed any time disease progression is suspected. Patients should not discontinue treatment because of clinical signs of progression until it has been confirmed by radiologic assessment.

CRs and PRs must be confirmed by repeated measurement at least 28 days and not more than 42 days after initial documentation. Patients who stop treatment following an unconfirmed response should also still have a confirmatory scan, if the scan can take place prior to the patient starting any subsequent anti-cancer therapies. If a patient is found to have a response at the confirmatory scan which has improved from PR to CR, then the improved response must also be confirmed within the pre-specified 28- to 42-day window, if the scan can take place prior to the patient starting any subsequent anti-cancer therapy.

In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval of not less than 7 weeks from baseline.

11 STATISTICAL CONSIDERATIONS

All statistical analyses will be performed using SAS[®], Version 9.3 or higher.

Unless specified otherwise, all data from each study part (Phase Ib and Phase II) will be presented separately in the tables, figures and listings.

The study database will be locked prior to the primary analyses for inclusion in the clinical study report (CSR). However, interim data will be made available to the SRC to assist with the identification of DLTs and enable dose escalation decisions whilst the study is ongoing.

11.1 Sample size and Statistical Analyses

In Phase Ib, approximately 6-12 evaluable patients will be enrolled in a 3+3 dose escalation design to determine the recommended dose for NUC-3373 in combination with docetaxel.

In Phase II, a Simon's two-stage design ([Simon, 1989](#)) will be used. The null hypothesis that the true response rate is 5% will be tested against a one-sided alternative. In the first stage, 13 patients will be accrued. If there are no responses in these 13 patients, the cohort will be stopped. Otherwise, 14 additional patients will be accrued for a total of 27 patients. The null hypothesis will be rejected if 4 or more responses are observed in 27 patients. The design yields a type I error rate of 0.04 and power of 0.8 when the true response rate is 20%.

11.2 Missing, Unused and Spurious Data

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 parameter, then the last screening value will be used as baseline. This value will also be used for calculations of changes from baseline. Unless otherwise defined, baseline will be defined as C1D1.

11.3 Analysis Populations

The analysis populations defined for this study are detailed below. In addition, and as deemed warranted by the data, efficacy may also be assessed in sub-populations as defined by the Sponsor. Subgroup analyses may 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 subgroup.

11.3.1 Safety Population

For each phase of the study, the Safety Population includes all patients in that phase of the study who received any study treatment 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.

11.3.2 Full Analysis Set

For each phase of the study, the Full Analysis Set (FAS) is based on the intention-to-treat principles and includes all patients who received at least one dose of study treatment. Patients will be included in the FAS based on the dose of study treatment initially received, regardless of any subsequent dose adjustments.

The FAS will be used to assess PFS and OS.

11.3.3 Evaluable for Response Population

The Evaluable for Response (EFR) population 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 over the two cycles, and undergone a post-treatment objective disease assessment.

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

11.3.4 PK Analysis Population

The PK Population contains all patients who received NUC-3373 as per protocol (*i.e.*, intended dose) and provided at least one usable PK profile. All PK data will be analysed according to treatment received.

This population will comprise all patients who received study treatment as per protocol (*i.e.*, intended dose) and did not violate or deviate from the protocol and planned dosing regimen in ways that would significantly affect the PK analyses (*e.g.*, skipping doses, or taking reduced doses or taking concomitant medications with the potential to cause a drug-drug interaction) during the PK sampling period. Patients who did deviate from the planned dosing regimen may still provide some data for inclusion in the PK set if they have at least one usable PK profile. The population and decisions regarding which profiles are usable will be defined by the study team, pharmacokineticist and statistician prior to any analyses being performed.

11.4 Statistical Methods

11.4.1 Patient Disposition

The disposition of patients will be summarised presenting the number of patients enrolled, the number of patients treated, the number of patients for whom the study drug was discontinued with the reasons for discontinuation, and the number of patients who discontinued participation in the study.

The number and percentage of patients included in each analysis population (as defined in [Section 11.3](#)) will be presented.

Patients with major protocol deviations or other significant deviations as defined in the SAP will be listed and summarised by dose cohort and overall.

11.4.2 Demographics 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.

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.

Relevant medical history and prior treatment for relevant indication, including, but not limited to systemic therapies, radiation and surgeries, will be listed and summarised using appropriate descriptive statistics. Full details will be provided in the SAP.

11.4.3 Concomitant Medications

Concomitant medication, coded using World Health Organisation Drug Dictionary (WHO DD) by WHO DD anatomical, therapeutic, chemical class and preferred term, will be listed. Summaries may be produced for concomitant medications of specific interest, as determined by the study team physician, for example use of haematopoietic growth factors and transfusions.

11.4.4 Extent of Exposure

Descriptive statistics for patients treated, including the number of infusions received, total dose given, and infusions delayed or missed, will be presented.

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

11.4.5 Safety Analysis

Safety analyses in addition to those described in the following subsections may be determined at any time without prejudice in order to most clearly enumerate rates of toxicities and to define further the safety profile of NUC-3373 + LV and docetaxel.

11.4.5.1 Adverse Events

AEs will be considered treatment-emergent (TEAE) 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. AEs will be summarised by Medical Dictionary for Regulatory Activities (MedDRA)TM System Organ Class (SOC) and preferred term, the latest version of MedDRA will always be used. The severity of AEs will also be summarised by CTCAE v5.0 (or higher) grade. Non-treatment-emergent AEs will be included in the patient listings and flagged as such but will not be included in the summary tables. Where an AE date is partial or missing, and it is unclear whether the AE is treatment-emergent, the AE will be assumed to be treatment-emergent.

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

- An overview table of the incidence of TEAEs, Grade 3+ TEAEs, SAEs, treatment-related TEAEs, TEAEs leading to treatment discontinuation and TEAEs leading to death, by dose 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 treatment-related 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, 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 SAEs by preferred term
- Summary of SAEs sorted in descending order of frequency

Additionally, the following will be listed:

- 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 SAEs 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 AE is resolved), Investigator's assessment of severity and relationship to study drug(s)
- 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

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 tabulations of AE data

11.4.5.2 Laboratory Parameters

Clinical laboratory data (actual and change from baseline) for continuous parameters at each scheduled assessment will be summarised using descriptive statistics including number of observations, mean, standard deviation, interquartile range (for overall only), minimum, median and maximum values. For categorical laboratory assessments, shift from baseline will be summarised using frequency and proportion at each scheduled assessment time.

Additionally, data may be displayed graphically. Full details will be provided in the SAP.

All clinical laboratory data for individual patients will be listed.

11.4.5.3 Vital Signs

All data will be listed and will be summarised for each scheduled assessment using descriptive statistics including number of observations, mean, standard deviation, interquartile range (for overall only), minimum, median and maximum values.

11.4.5.4 ECOG Performance Status

ECOG performance status will be listed. The ECOG Performance Scale is provided in Appendix 3 of the core protocol.

11.4.5.5 Physical Examination

Full physical examination includes ears, eyes, nose, head, throat, neck, lungs, heart, abdomen, extremities, skin, musculoskeletal, nervous system, and lymph nodes.

Listings will be provided for physical examination parameters.

11.4.5.6 ECGs

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.

All ECG data will be listed. In addition, ECG parameters including, but not limited to QT and QTc, will be summarised by visit summarising both absolute values and the change from baseline.

11.4.6 Pharmacokinetic Analysis

The PK of NUC-3373 will be assessed, including:

- $C_{\max}$
- AUC
- $t_{1/2}$
- V_d
- CL

The plasma analytes measured may include, but are not limited to NUC-3373, 5-FU, FBAL, dUrd.

All PK parameters will be analysed in the PK population.

11.4.7 Efficacy Analysis

11.4.7.1 Change from Baseline in Tumour Size

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

- Baseline tumour size ($TS_{baseline}$): sum of longest diameters of target lesions at baseline
- On-study TS ($TS_{timepoint}$): sum of longest diameters of target lesions at a post-treatment disease assessment timepoint

$$\% \Delta TS_{\text{timepoint}} = \frac{TS_{\text{timepoint}} - TS_{\text{baseline}}}{TS_{\text{baseline}}} \times 100$$

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

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

- Baseline tumour size (TS_{baseline}): sum of longest diameters of target lesions at baseline
- Best TS (TS_{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

$$\% \Delta TS_{\text{best}} = \frac{TS_{\text{best}} - TS_{\text{baseline}}}{TS_{\text{baseline}}} \times 100$$

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

Tumour size ($\% \Delta TS_{\text{Wk8}}$ and $\% \Delta TS_{\text{best}}$) 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. 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 PR, respectively.

11.4.7.2 Objective Response Rate

ORR is defined as the number of patients achieving a confirmed response (CR or PR) in accordance with RECIST v1.1 criteria (see Appendix 1 of the core protocol). The number and percentage of patients in each RECIST v1.1 response category (CR, PR, SD, progressive disease or not evaluable [NE]), as well as the ORR will be presented.

All data will be summarised and listed.

11.4.7.3 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.

All data will be summarised and listed.

11.4.7.4 Duration of Response

DoR is defined 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 recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started). 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 time point of analysis without a known record of death or progression, the DoR will be censored

at the date of last tumour assessment. DoR will be assessed in the subset of the EFR population categorised as responders for the assessment of ORR.

DoR will be listed and may be summarised if there are sufficient responders.

11.4.7.5 Duration of Stable Disease

SD is defined for the subset of the EFR population categorised as having neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease. Duration of SD is defined as the time, in days, from the first dose of study treatment (C1D1) 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.

Duration of SD will be listed and may be summarised if there are sufficient responders.

11.4.7.6 Progression-Free Survival

PFS is defined as the time from first dose of study treatment (C1D1) 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 v1.1 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 v1.1 assessment.

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 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 v1.1 assessment in the absence of progression.

The number of overall censored patients, number of patients with events and Kaplan-Meier estimates median time will be provided. In addition, the results will be presented graphically in Kaplan-Meier plots.

11.4.7.7 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.

11.5 Primary and Interim Analyses

The analysis of safety for a cohort will take place when all of the enrolled patients have completed the first two treatment cycles 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. To enable the SRC to make dose escalation decisions, safety and tolerability data will be reviewed on an ongoing basis. There will be no formal requirements for a database lock to support these ongoing reviews. Upon review of the safety and tolerability data from each cohort by the SRC, additional patients may be added to a cohort to further evaluate the safety profile of the combination.

11.6 Changes to the Planned Statistical Methods

Any changes to the planned statistical methods from those specified in the final SAP will be documented in the CSR.

12 REFERENCES

- Baldwin CM & Perry CM. pemetrexed. *Drugs* 2012; 69:2279-2302.
- Cersosimo RJ. Lung cancer: A review. *Am J Health-Syst Pharm* 2002; 59:611-642.
- Chen Z *et al.* Non-small-cell lung cancers: a heterogenous set of diseases. *Nat Rev Cancer* 2014; 14:535-546.
- Constenla M *et al.* Docetaxel, 5-fluorouracil, and leucovorin as treatment for advanced gastric cancer: results of a phase II study. *Gastric Cancer* 2002; 5:142-147.
- Docetaxel Summary of product Characteristics. 11 March 2022. Available from: <https://www.medicines.org.uk/emc/product/7206/smpc#gref>
- Duma N *et al.* Non-small cell lung cancer: Epidemiology, screening, diagnosis, and treatment. *Mayo Clin Proc* 2019; 94:1623-1640.
- Esteban E *et al.* Prospective randomised phase II study of docetaxel versus paclitaxel administered weekly in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. *Ann Oncol* 2003; 14:1640-1647.
- Ferlay J *et al.* Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015; 136:E359-E386.
- Ghazaly E *et al.* Interim pharmacokinetic and pharmacodynamic data from the first-in-human study of NUC-3373, a pyrimidine nucleotide analogue, in patients with advanced solid tumours. *Annals of Oncology* (abstracts developmental therapeutics) 2017; 28 (Suppl. 5):V128.
- GlobalData. Non-small cell lung cancer: Global drug forecast and market analysis to 2029. December 2020.
- Hamada C *et al.* Meta-analysis of postoperative adjuvant chemotherapy with tegafur-uracil in non-small cell lung cancer. *J Clin Oncol* 2005; 23:4999-5006.
- Hanna N *et al.* Randomized phase III trial of pemetrexed *versus* docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. *J Clin Oncol* 2004; 22:1589-1597.
- Hofheinz R-D *et al.* Trastuzumab in combination with 5-fluorouracil, leucovorin, oxaliplatin and docetaxel as perioperative treatment for patients with human epidermal growth factor receptor 2-positive locally advanced esophagogastric adenocarcinoma: A phase II trial of the Arbeitsgemeinschaft Internistische Onkologie Gastric Cancer Study Group. *Int J Cancer* 2021; 149:1322-1331.
- Ichinose Y *et al.* S-1 plus cisplatin combination chemotherapy in patients with advanced non-small cell lung cancer: a multi-institutional phase II trial. *Clin Cancer Res* 2004; 10:7860-7864.
- Kato H *et al.* Japan Lung Cancer Research Group on Postsurgical Adjuvant Chemotherapy: A randomized trial of adjuvant chemotherapy with uracil-tegafur for adenocarcinoma of the lung. *N Engl J Med* 2004; 350:1713-1721.
- Liu Y *et al.* Expression of thymidylate synthase predicts clinical outcomes of pemetrexed-containing chemotherapy for non-small-cell lung cancer: a systemic review and meta-analysis. *Cancer Chemotherapy and pharmacology* 2013; 72:1125-1132.

NCCN guidelines for non-small cell lung cancer. Version 1.2022. 07 December 2021. Available from: <https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1450>.

Paz-Ares L *et al.* Phase III trial comparing paclitaxel poliglumex vs docetaxel in the second-line treatment of non-small cell lung cancer. *British J Cancer* 2008; 98:1608-1613.

Shintani Y *et al.* Low dihydropyrimidine dehydrogenase correlates with prolonged survival in patients with lung adenocarcinoma treated with 5-fluorouracil. *Anticancer Research* 2011; 31:4665-4672.

Siddiqui MA *et al.* Thymidylate synthase drives the phenotypes of epithelial-to-mesenchymal transition in non-small cell lung cancer. *BJC* 2021; 124:281-289.

Simon R. Optimal two-stage designs for phase II clinical trials. *Control Clin Trials* 1989; 10:1-10.

Taxotere Prescribing Information. December 2013. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/020449s071lbl.pdf.

Tomasini P *et al.* Pemetrexed for advanced stage nonsquamous non-small cell lung cancer: latest evidence about its extended use and outcomes. *Ther Adv Med Oncol* 2016; 8:198-208.

Tominga T *et al.* Epidermal growth factor signals regulate dihydropyrimidine dehydrogenase expression in EGFR-mutated non-small-cell lung cancer. *BMC Cancer* 2016; 16:354.