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STATISTICAL ANALYSIS PLAN

A Randomized, Open-label Phase 2 Study of Nanoliposomal Irinotecan (nal-IRI)-containing Regimens *versus* nab-paclitaxel plus Gemcitabine in Patients with Previously Untreated, Metastatic Pancreatic Adenocarcinoma

PROTOCOL VERSION AND DATE: VERSION 7.0 – 27 SEPTEMBER 2019

SAP Version	Date
Final Version 3.0	May 10, 2021

STUDY NUMBER:	MM-398-07-02-03
EUDRACT NUMBER	2015-003086-28
PROTOCOL TITLE:	**A Randomized, Open-label Phase 2 Study of Nanoliposomal Irinotecan (nal-IRI)-containing Regimens *versus* nab-paclitaxel plus Gemcitabine in Patients with Previously Untreated, Metastatic Pancreatic Adenocarcinoma**
SAP VERSION:	Final Version 3.0
SAP DATE:	May 10, 2021

Further to your review and agreement to the Statistical and Analysis Plan version indicated above, please sign to indicate approval for your area of responsibility:

RESPONSIBILITY	NAME, TITLE & OFFICE	SIGNATURE	DATE
PPD	Ipsen PPD PPD Ipsen Bioscience, Inc. 650 East Kendall Street Cambridge, MA 02142)		18May2021

RESPONSIBILITY	NAME, TITLE & OFFICE	SIGNATURE	DATE
PPD	CCI PPD		

IMPORTANT: This completed record (with additional sheets, where required), confirms the above-mentioned Statistical and Analysis Plan version became the Final Statistical and Analysis Plan

History of Changes				
Version Date		**02 DECEMBER 2019 (VERSION 2.0)**	**10 MAY 2021 (VERSION 3.0)**	**Reason for Change**
Page	**Section**	**Was**	**Is**	
8	1.1	Protocol Deviation Specification, Version 5.0 (February 28, 2019)	Protocol Deviation Specification, Version 7.0 (September 30, 2020)	New document release
24	3.2.1.1	Progression documented within 16 weeks of baseline or last the CCI [redacted] CCI [redacted]	Progression documented prior to new anti-cancer therapy within 16 weeks CCI [redacted] CCI [redacted]	Sponsor requests
24	3.2.1.1	Death documented within 16 weeks of baseline or last the CCI [redacted] CCI [redacted]	Death documented prior to new anti-cancer therapy within 16 weeks of baseline CCI [redacted] CCI [redacted]	Sponsor requests
24	3.2.1.1		Add two new censoring rules: Progression documented after new anti-cancer therapy Death documented after new anti-cancer therapy	Sponsor requests

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

5-FU:	5-Fluorouracil
AD:	Analysis Dataset
AE:	Adverse Event
ALT (SGPT):	Alanine Aminotransferase
AST (SGOT):	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC:	Area Under the Curve
BMI:	Body Mass Index
BOR:	Best Overall Response
BSA:	Body Surface Area
Cavg:	Average concentration
Cmax:	Maximum concentration
Cmin:	Minimum concentration
CA19-9:	Carbohydrate antigen 19-9
CBC:	Complete Blood Count
CR:	Complete Response
CRF:	Case Report Form
CRO:	Clinical Research Organisation
CTCAE:	Common Terminology Criteria for Adverse Events
DCR:	Disease Control Rate
DCR_{16}:	Disease Control rate at 16-Week
DLT:	Dose-Limiting Toxicity
DLTs:	Dose-Limiting Toxicities
eCRF	electronic Case Report Form
ECG:	Electrocardiogram
EoS:	End of Study
EoT:	End of Treatment
EP:	Enrolled Population
GDO:	Global Data Operation
mmHg:	Millimetres of Mercury
HR:	Heart Rate
in:	inch
ICH:	International Conference on Harmonisation
ITT:	Intention-To-Treat
kg:	kilogram
KPS:	Karnofsky Performance Status

lb:	pounds
MedDRA:	Medical Dictionary for Regulatory Activities
min:	minute
msecs:	milliseconds
nal-IRI:	Nanoliposomal irinotecan; MM-398
NCI:	National Cancer Institute
NCI-CTC:	National Cancer Institute – Common Toxicity Criteria
LV:	Leucovorin
ORR:	Over Response Rate
OS:	Overall survival
PD:	Progression of Disease
PFS	Progressive free Survival
PK:	Pharmacokinetic
PP:	Per Protocol
PR:	Partial Response
PT:	Preferred Term
QC:	Quality Check
QRS:	QRS interval duration
QT:	Time interval for ventricular depolarisation and repolarisation
QTc:	Corrected QT interval
QTcF:	QT interval, Fridericia correction
RECIST	Response Evaluation Criteria In Solid Tumors
SAP:	Statistical and Analysis Plan
SAE:	Serious Adverse Event
SAF:	Safety Population
SAS®:	Statistical Analysis System®
SD:	Stable Disease
SI:	Standard International
SOC:	System Organ Class
SOP:	Standard Operating Procedure
TE:	Treatment-Emergent
TEAE:	Treatment-Emergent Adverse Event
WBC:	White Blood Cell
WHO-DD:	World Health Organization – Drug Dictionary

1 INFORMATION TAKEN FROM THE PROTOCOL

1.1 Introduction

Metastatic pancreatic cancer patients have a very poor prognosis and low median survival rates (< 1 year), necessitating the need for new treatment options. Nanoliposomal irinotecan; MM-398 (nal-IRI) is a novel agent which has demonstrated efficacy in the Phase 3 NAPOLI-1 trial, in patients with metastatic pancreatic cancer previously treated with gemcitabine. This study will examine the safety, tolerability, and preliminary efficacy of nal-IRI in combination with 5-Fluorouracil/ Leucovorin (5-FU/LV) and oxaliplatin, in patients not previously treated for metastatic pancreatic adenocarcinoma.

This SAP is based upon the following study documents:

- Study Protocol, Version 7.0 (September 27, 2019)
- electronic Case Report Form (eCRF), Version 8.0 (July 9, 2018)
- Protocol Deviation Specification, Version 7.0 (September 30, 2020)

1.2 Study objectives

1.2.1 Primary objectives

The primary objectives of this study are:

- To evaluate the safety and tolerability of nal-IRI + 5-FU/LV + oxaliplatin
- To characterize Dose-Limiting Toxicities (DLTs) associated with nal-IRI + 5-FU/LV + oxaliplatin and determine the recommended dose of the triplet combination for future development

1.2.2 Secondary objectives

The secondary objectives of this study are:

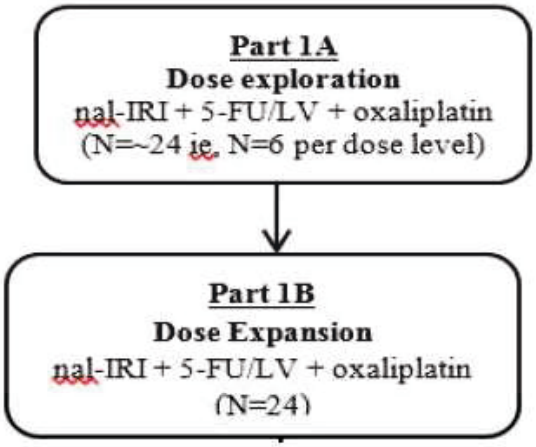
- To characterize the Pharmacokinetics (PK) of nal-IRI in combination with 5-FU + oxaliplatin
- To evaluate efficacy signals with nal-IRI in combination with 5-FU/LV + oxaliplatin using overall response rate (ORR) [Complete Response (CR) + Partial Response (PR), per Response Evaluation Criteria In Solid Tumors (RECIST) v1.1], disease control rate (DCR) [CR + PR + Stable Disease (SD), per RECIST v1.1], duration of response, Progression-free survival (PFS), best overall response (BOR) and Overall survival (OS)

1.3 Overall study design plan

This is an open-label, phase 2 study to assess the safety, tolerability, and preliminary efficacy of nal-IRI in combination with 5-FU/LV and oxaliplatin in patients not previously treated for metastatic pancreatic adenocarcinoma.

The study will be conducted, as illustrated in the schematic below, with an initial dose exploration (Part 1A) followed by dose expansion (Part 1B) of the nal-IRI + 5-FU/LV + oxaliplatin regimen.

Figure 1 Overview of Study Design



All PK, pharmacogenomic, pharmacodynamics and biomarker analysis in Part 1 will be detailed in a separate document when applies.

In Part 1A safety and tolerability will be evaluated across a range of oxaliplatin and nal-IRI dose permutations, as summarized in Table 1. Oxaliplatin will be administered at intended dose levels of 60 mg/m^2 - 85 mg/m^2 IV over 120 minutes (±10 minutes), on Days 1 and 15 of each 28-day cycle. Nal-IRI will be administered at a dose range of 60 mg/m^2 – 80 mg/m^2 IV over 90 minutes (±10 minutes), on Days 1 and 15 of each cycle. 5-FU and leucovorin will be administered at fixed dose levels (2400 and 400 mg/m^2 respectively) for all dose level cohorts.

Table 1 Part 1 Dose Escalation Table (Nal-IRI + 5-FU/LV + Oxaliplatin)

Evaluation Status	Dose Level	Oxaliplatin		5-FU/LV		Nal-IRI	
		Dose (mg/m^2)	Dose Day[a]	Dose (mg/m^2)	Dose Day[a]	Dose (mg/m^2)[b]	Dose Day[a]
Evaluation complete	1	60	1, 15	2400/400	1, 15	80	1, 15
Evaluation complete	-1	60	1, 15	2400/400	1, 15	60	1, 15
Not to be evaluated	2	CCI					
Not to be evaluated	-2A						
Evaluation complete	-2B	85	1, 15	2400/400	1, 15	60	1, 15
New dose level to be evaluated	-3	70	1, 15	2400/400	1, 15	65	1, 15

[a] Day indicated is part of a 28-day cycle
[b] Nal-IRI the dose is calculated in salt base.
Note: The dose of nal-IRI and 5-FU/LV in Dose Level 1 and 2 above is the same dose and schedule that was previously used in the NAPOLI-1 Phase 3 study.

Part 1A will enroll cohorts of patients following a 3 + 3 dose escalation design, in order to select the dose level of the combination of oxaliplatin and nal-IRI to be used in Part 1B (dose expansion). Dose limiting toxicities, as defined in the Study Protocol Amendment v7.0 Section 3.2.2 and in SAP section 1.3.1, will be assessed during the safety evaluation period (i.e. 28 days in Cycle 1; or 14 days after the 2nd dose of study treatment if there is a treatment delay according to the Study Protocol Amendment v7.0 Section 6.5).

Safety evaluations are to be conducted regularly by the DLT committee to review all serious adverse events (SAEs), adverse events (AEs) and DLTs for each patient to determine the safety and tolerability in each Cohort. The DLT Committee is comprised of the Investigators, the Medical Monitor, and the Sponsor.

In the absence of Dose-Limiting Toxicity (DLT), a minimum of 3 patients will be treated within each dose level cohort for a minimum of one cycle of therapy. Additional patients will be recruited into a cohort according to the DLT provisions outlined in the Study Protocol Amendment v7.0 Section 3.2.2 and in SAP section 1.3.1, or if non-DLT toxicity is identified as requiring further evaluation by the DLT Committee.

In each dose level cohort, if there are no DLTs within the safety evaluation period, then additional dose level cohorts will be initiated following agreement by the DLT Committee. If CCI

As DLT within any cohort is potentially determined by a complex interaction between the respective dose levels of oxaliplatin and nal-IRI, the sequence of cohorts examined (dose levels -1 to -3) contains both dose escalation and dose de-escalation strategies for each individual drug, in order to control the total *combined* dose level within any given cohort. This means that for each individual drug, the dose level may decrease, increase or remain the same between successive cohorts.

The Protocol Amendment v5.0 introduces a new dose level cohort in Part 1A (dose level -3: oxaliplatin 70 mg/m^2 + nal-IRI 65 mg/m^2) to evaluate its safety and tolerability. Prior to this amendment, the enrolment of dose level cohorts 1, -1 and -2B has been completed. Dose levels 1 and -2B were considered to be not tolerable. Dose level 1 (oxaliplatin 60 mg/m^2 + nal-IRI 60 mg/m^2) was determined to be safe and tolerable. Following the completion of the three predefined dose level cohorts, this protocol amendment introduces a new dose level -3 (oxaliplatin 70 mg/m^2 + nal-IRI 65 mg/m^2) for evaluation. CCI CCI

At the completion of the safety evaluation period for dose level cohorts -1 to -3 (Part 1A) detailed in Table 1, all available data (DLT, Serious Adverse Event (SAE), and grade 3-4 adverse events (AEs), any available pharmacokinetic (PK), pharmacogenomic, pharmacodynamic results and any initial efficacy data) are reviewed by the DLT Committee. A dose level will be selected for expansion (Part 1B as described below). The expansion cohort is intended to enroll 24 additional patients (total of 30 patients for the selected dose level) to obtain additional safety and efficacy data.

- If the dose level cohort -3 (oxaliplatin 70 mg/m^2 + nal-IRI 65 mg/m^2) is considered to meet the safety and tolerability criteria, this dose will be selected for expansion.
- If the dose level cohort -3 is not considered to meet the defined safety and tolerability criteria, the dose level cohort -1 (oxaliplatin 60 mg/m^2 + nal-IRI 60 mg/m^2) will be selected for expansion.

No DLT assessment will be conducted for the expansion cohort.

Final determination of an appropriate combination regimen for potential future development will be made after all patients in the Part 1A (dose escalation) and Part 1B (expansion cohort) have completed two scheduled assessments (approximately 16 weeks of therapy; unless withdrawn at an earlier time point due to disease progression or drug-related toxicity) and will take into account all available data from the expansion cohort and also all available updated data for patients still receiving ongoing therapy in the other dose level cohorts.. Data will include DLT, SAE, and grade 3-4 adverse events along with any available PK, pharmacogenomic, pharmacodynamic results and any initial efficacy data.

For the extension phase of the study, patients will continue to be followed for OS every 4 months. Patients still receiving treatment will continue to receive this until disease progression, death, unacceptable study medication related toxicity or withdrawal of consent.

For patients receiving treatment in the extension phase of the study only OS and treatment-related SAEs will be collected in the eCRF. In the event that an SAE occurs, additional information (such as local laboratory results, concomitant medications, and procedures) may be requested by the Sponsor in order to evaluate the reported SAE, though this additional information does not need to be captured in the eCRF. Investigators may perform standard procedures and tests needed to treat and evaluate patients; however, the results of these assessments will not be routinely reported. The extension phase of the study will be completed once all patients have died, withdraw consent, or lost to follow-up after two attempts on OS follow-up.

1.3.1 Dose limiting toxicities (DLTs)

For nal-IRI administered in combination with 5-FU/LV and oxaliplatin, the following adverse events will be considered as dose limiting toxicities (DLTs) if they occur during the safety evaluation period (i.e. 28 days of Cycle 1; or 14 days after the 2nd dose of study treatment if there is a treatment delay according to the Study Protocol Section 6.5) and are deemed related to the study treatment regimen.

- Grade 4 neutropenia or thrombocytopenia that does not resolve within 7 days despite optimal therapy (withholding study treatment and administering concomitant medication, e.g. G-CSF administration for neutropenia)
- Grade 4 neutropenia complicated by fever ≥ 38.5 °C (i.e. febrile neutropenia) and/or Grade 3 neutropenia with infection
- Any study regimen related adverse event that leads to a delay of the next scheduled study treatment dose for more than 14 days
- Any grade 4 non-hematologic toxicity with the specific *exclusion* of:
  - Fatigue/asthenia < 2 weeks in duration
  - Increases in alkaline phosphatase levels
  - Nausea and vomiting ≤3 days duration (only considered dose limiting if they last > 72 hours after treatment with an optimal anti-emetic regimen)
  - Diarrhea ≤3 days duration (only considered dose limiting if diarrhea lasts > 72 hours after treatment with an optimal anti-diarrheal regimen)

Any adverse event that is related to disease progression will not be considered a DLT.

As part of this study, pharmacogenomic data will be collected on all patients for determination of UGT1A1*28 status. UGT1A1*28 allele status may be considered when evaluating DLTs. This will be detailed in a separate document when applies.

To be DLT evaluable, a patient should have received both Cycle 1 doses of study medication. A delay of up to 14 additional days (a total of 28 days) is permitted between the scheduled Day 1 and Day 15 administrations due to non-DLT treatment related toxicity. Section 1.4.1.3 displays for the guidance of patient replacement in Part 1 (dose level cohorts -1 to -3).

The final determination of DLTs will be made following discussion by the DLT Committee (comprising the Part 1 Investigators, the Medical Monitor, and the Sponsor).

All patients will continue to be monitored for safety beyond Cycle 1, in order to determine if multiple cycles of treatment are tolerable.

If any patient within a given cohort experiences a DLT in Part 1A, they may continue in the study at a lower dose level of oxaliplatin and/or nal-IRI, (as determined by the DLT Committee in accordance with the Study Protocol Section 6.5) upon resolution of the relevant toxicity. Other patients in the same cohort who do not experience a DLT will continue with unmodified dose levels of oxaliplatin and/or nal-IRI (unless a dose modification is judged to be necessary by the DLT Committee on safety grounds).

In Part 1A and Part 1B, patients within any given cohort will remain on the dose levels of oxaliplatin and nal-IRI they were originally allocated to. Dose escalation within a cohort will not be permitted, although dose modifications for toxicity will occur in accordance with the Study Protocol Section 6.5.

1.3.2 Study population

According to safety and efficacy parameters, patient populations defined for this study are described below:

- Enrolled population (EP): This population includes patients who have successfully completed screening and have documented enrollment date in the study.
- Safety population (SAF): The safety population includes patients receiving at least one dose of any study treatment.
- PK Population: The PK population will include all nal-IRI treated patients which received at least 1 dose, and who had at least 1 plasma concentration and no major protocol deviations affecting PK variables.

1.3.3 Study exposure

The planned doses will be per Table 1, Oxaliplatin, 5-FU and nal-IRI will be administered on Days 1 and 15 of each 28-day cycle as below:

- Oxaliplatin will be administered at dose levels as indicated in Table 1 (60 mg/m^2 - 85 mg/m^2), IV over 120 minutes (±10 minutes), on Days 1 and 15 of each 28-day cycle. Nal-IRI will be administered over a dose range 60 mg/m^2 – 80 mg/m^2 IV over 90 minutes (±10 minutes), on Days 1 and 15 of each 28-day cycle

- 5-FU will be administered 2400 mg/m^2 IV over 46-hours (±60 minutes), on Days 1 and 15 of each 28-day cycle with leucovorin (l + d racemic form) 400 mg/m^2, IV over 30 minutes (±5 minutes), on Days 1 and 15 of each 28-day cycle.

The expected and actual doses received and detailed administration will be collected in the CRF.

1.4 Methods and procedures

1.4.1 Subject identification and allocation to study treatment

Patients who are confirmed to meet all inclusion and exclusion criteria will be enrolled in the study and receive the first dose (Cycle 1 Day 1).

It is expected that multiple sites will participate in this trial. Enrolment will be based on the availability of patients at each site and the availability of slots in each cohort. Slots must be confirmed by the Sponsor, or designee, prior to consenting patients to the study. A reasonable attempt will be made to equally distribute patients between sites. Enrolment can proceed to the next cohort after the safety data from the safety evaluation period in the previous cohort have been evaluated in accordance with Section 1.4.1.1 and 1.4.1.2 below:

1.4.1.1 Decision process for cohort progression

Decisions to progress to the next dose level cohort will be made by mutual agreement of the DLT Committee (in accordance with the criteria described below (Section 1.4.1.2)). Regularly scheduled teleconferences of the DLT Committee will serve as a forum for ongoing review of safety and other relevant data. Decisions to progress to the next dose level cohort must be agreed by the majority of the DLT Committee members and will be documented along with a summary of the information supporting the decision.

1.4.1.2 Decision criteria for cohort progression

The safety assessment period for purposes of DLT evaluation and dose level cohort progression decisions will be one cycle of treatment (i.e. 28 days of Cycle 1; or 14 days after the 2nd dose of study treatment if there is a treatment delay according to the Study Protocol Amendment v7.0 Section 6.5). Progression to the next dose level cohort will only occur after all available safety and other relevant data have been evaluated for the current dose level cohort (once the last patient enrolled in the cohort completes the safety evaluation period). Potential data which may be reviewed by the DLT Committee for the purposes of dose level assessment include DLT, SAE, and grade 3-4 adverse events, any available pharmacokinetic, pharmacogenomic, pharmacodynamic results and any initial efficacy data.

In addition, any treatment-related toxicities of Grade 3 or higher occurring after Cycle 1 of each cohort will be assessed by the DLT Committee on an ongoing basis for their potential

relationship to cumulative toxicity of one or more study agents and will be considered in decisions to progress to subsequent dose level cohorts.

1.4.1.3 Patient replacement

For Part 1A (dose level cohorts -1 to -3), any patient requiring a dose delay of >14 days during the safety evaluation period due to nondrug related reasons will be replaced for DLT evaluation purposes. Any patient not receiving both doses of study treatment during the safety evaluation period, for reasons other than dose limiting toxicity, will be replaced for DLT evaluation purposes.

For Part 1B (the expansion period), patients withdrawing from treatment with study medication will not be replaced.

1.4.2 Subjects assessments

1.4.2.1 Efficacy assessments

Efficacy in the study will include PFS, ORR, duration of response, DCR at 16 weeks, BOR and OS.

PFS time will be determined as the time from date of first study treatment to the first documented radiographical progression of disease (PD), per investigator using RECIST v1.1, or death from any cause, whichever comes first. PFS will be descriptively summarized for each dose level cohort and combined selected dose level cohort.

Best Overall Response (BOR) is defined as the best response as recorded from the start of study treatment until disease progression or start of new anti-cancer therapy. Summary of BOR will be displayed for each dose level cohort and combined selected dose level cohort.

ORR is defined as the proportion of patients with a BOR characterized as either a Complete Response (CR) or Partial Response (PR) relative to the total number of evaluable patients. Evaluable patients are the treated patients with measurable disease at baseline.

The disease control rate (DCR) is defined as proportion of patients with CR or PR or SD, per RECIST v1.1 relative to total number of treated patients with measurable disease at baseline. The disease control rate at 16-week (DCR_{16}) assessment for each dose level cohort will be estimated as DCR at 16 weeks assessment.

Overall Survival (OS) is the time from date of first study treatment to the date of death from any cause. Patients who are alive or lost to follow-up at the time of the analysis will be censored at the last known alive date. OS will be summarized for each dose level cohort.

Duration of Response (DoR) is defined as the time from the first date of response (CR or PR) to first date of documented radiographical PD, per investigator using RECIST v1.1.

1.4.2.2 Safety assessments

Safety analyses will include all treated patients (using the safety population (SAF)) and will be based on adverse events, laboratory data, and study treatment related dose-limiting toxicities. Adverse events will be reported by the Medical Dictionary for Regulatory Activities (MedDRA) version 20.1 or higher. Toxicity will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

Safety analysis of patients in this SAP will include:

The period for treatment-emergent adverse events and safety findings will be from the time of first study treatment administration to 30 days after the date of last study treatment administration. If an adverse event begins on the date of first study treatment administration with no time recorded, the event will be considered as treatment emergent.

Tabular summaries will be presented for all adverse events, pre-treatment adverse events, treatment-emergent adverse events (TEAE), serious adverse events, adverse events leading to study treatment discontinuation, TEAE-related to study treatment and TEAE Grade 3/4. Adverse events will be summarized by System Organ Class and preferred term. All adverse event data will be listed by patient.

A summary of dose-limiting toxicity events will be provided.

Laboratory data will be presented by cycle. Abnormal laboratory values will be assessed using all available data and toxicity grading will be assigned according to NCI CTCAE version 4.03 toxicity scale, where criteria are available to do so. Laboratory, vital signs, and 12-lead Electrocardiogram (ECG) data will be summarized according to parameter type.

1.4.2.3 Other assessments

A listing of PK sample will be displayed. Plasma concentrations of total irinotecan, SN-38, and 5-FU and oxaliplatin in the combination therapies will be used to characterize corresponding pharmacokinetic (PK) parameters using a nonlinear mixed effects approach (if warranted by the data). PK parameters for individual patients will be estimated based on the Empirical Bayesian Estimation method with priors from the previously published parameters. PK parameters such as C_{max}, AUC (area under the curve), C_{avg} and C_{min} will be derived from the model and compared to historical data in order to examine any possible interactions between nal-IRI and the combination therapies. Evaluation of the relationship between dose, PK, efficacy and safety endpoints might be performed after exploratory analysis. A detailed PK analysis plan will be described in a separate document and results will be captured in a standalone report.

1.4.2.4 Withdrawal/discontinuation

Discontinuation of study treatment

It is intended that patients will be treated until radiologically determined progressive disease per RECIST v1.1 or unacceptable study treatment related toxicity. However, a patient may

discontinue study treatment at any other time. Reasons for discontinuation of study treatment include, but are not limited to the following:

- Radiologically determined progressive disease, per RECIST v1.1
- Clinical deterioration sufficient to prevent further radiological assessment
- A study treatment related adverse event, prior to disease progression, which:
  - in the opinion of the Investigator, precludes further treatment with all study treatments
  - requires treatment with one or more study treatments to be withheld for more than 14 days, unless in the opinion of the investigator the patient is receiving benefit overall from the study treatment
  - would result in a third dose reduction in any study treatment (in a patient having already experienced 2 previous dose reductions)
  - requires discontinuation of nal-IRI (Arm I only)
- Development of an intercurrent medical condition or need for concomitant therapy that precludes further treatment with all study treatments
- Withdrawal of consent for further treatment
- Pregnancy

A patient who discontinues study medication has not withdrawn from the study and must continue with all ongoing protocol requirements.

Withdrawal from the study

A patient may withdraw, or be withdrawn, from the study at any time. Reasons for withdrawal from the study include, but are not limited to the following:

- Significant noncompliance with the protocol, per Investigator's assessment,
- The Investigator removes the patient from the trial in the best interests of the patient,
- Use of prohibited concomitant medications,
- Patient is lost to follow up,
- Withdrawal of consent for further participation in the study,
- Death,
- Study termination by the Sponsor.

Procedures following study treatment discontinuation or study withdrawal

Following study treatment discontinuation all procedures and evaluations required at the 30-day (End of Treatment) follow up visit should be completed. All patients who discontinue study medication as a result of an adverse event must be followed until resolution or stabilization of the adverse event. Patients who discontinue study treatment prior to radiologically determined disease progression should continue to be assessed radiologically, according to the protocol-specified schedule, until radiologically determined progressive disease per RECIST v1.1 has been documented. Overall survival follow-up contacts should continue every 2 months from the 30-day follow-up visit until death or study closure, whichever comes first.

If a patient does not return to the clinic for follow-up visits, attempts should be made to contact the patient via phone, email, or mail. At least 3 documented attempts, including one via certified mail, should be made to contact the patient before declaring a patient lost to follow-up. If the patient is considered lost to follow-up, the date of death may be captured from public records.

If a patient **withdraws from the study** at any point, a complete final evaluation at the time of the patient's withdrawal should be made with an explanation of the reason for withdrawal. At the time of withdrawal from the study, it should be clarified with the patient whether they still consent to be followed up for survival status only (including where appropriate through publicly available records) and any such consent to ongoing survival follow up must be documented in both the source hospital records and the CRF.

1.4.3 Planned sample size

The total number of patients enrolled in the study will depend on the number of patients examined within each dose level cohort, as determined by the DLT Committee. Progression to the next dose level cohort will depend on the background toxicity rate (i.e., probability of DLT at a given dose). When 1 of 3 patients develops a DLT and the cohort is expanded to a minimum of 6 patients, CCI

CCI

CCI

Approximately 54 patients will be enrolled in the study.

2 SUBJECT POPULATIONS (ANALYSIS SETS)

2.1 Enrolled Population (EP)

Enrolled population includes patients who have successfully completed screening and have documented enrollment date in the study.

2.2 Efficacy

2.2.1 Intention-To-Treat population (ITT)

No ITT population will be in Part 1 in this SAP.

2.2.2 Per protocol population (PP)

No PP population will be in Part 1 in this SAP.

2.3 Safety population (SAF)

Safety population includes patients receiving at least one dose of any study treatment.

2.4 Pharmacokinetics population (PK population)

The PK population will include all nal-IRI treated patients which received at least 1 dose, and who had at least 1 plasma concentration and no major protocol deviations affecting PK variables.

3 STATISTICAL METHODS

3.1 Statistical analysis strategy

The statistical analyses will be performed in accordance with ICH E9 guideline and will be based on the pooled data from the individual study sites, unless otherwise stated. The primary analysis will be performed when the last patient is followed for one year. The data used for the primary analysis will be cleaned and programmatically cut at the date of last patient followed for one year. Following fulfillment of analysis requirements for the primary and/or secondary endpoints, patients that are still receiving treatment or are being followed for OS to an extension phase of the study. The extension phase of the study will be completed once all patients have died, withdraw consent, or lost to follow-up after two attempts on OS follow-up. The descriptive summary of OS and treatment-related SAEs will be presented for patients in the extension phase of the study.

3.1.1 Primary efficacy endpoint

The primary efficacy endpoint is Progression-free survival (PFS).

PFS time will be determined as the time from date of first study treatment to the first documented radiographical progression of disease (PD), per investigator using RECIST v1.1, or death from any cause, whichever comes first. The censoring rules will be displayed in Section 3.2.1.

3.1.2 Secondary efficacy endpoints

The secondary efficacy endpoints are as stated within the protocol are:

(a) Best Overall Response (BOR)

BOR is defined as the best response as recorded from the start of study treatment until disease progression or start of new anti-cancer therapy. Patients without a post-baseline tumor assessment will be considered to be non-evaluable for BOR.

To classify BOR as stable disease (SD), there should be a qualifying SD assessment at least 6 weeks from enrolment.

(b) Overall Response Rate (ORR)

ORR is defined as the proportion of patients with a BOR characterized as either a Complete Response (CR) or Partial Response (PR) relative to the total number of evaluable patients. Evaluable patients are the treated patients with measurable disease at baseline.

(c) Disease Control Rate at 16-week (DCR_{16}) assessment

DCR_{16} for a treatment cohort will be estimated by the number of patients who achieve disease control at 16-week assessment divided by the number of patients treated.

Note that a patient will be classified as having achieved disease control at 16-week assessment if the patient has not progressed at the 16-week assessment, i.e. has no PD up to and including the 16-week assessment with documented non-PD (SD, PR, or CR) assessment. Patients, who die, discontinue tumor assessments, or start new anti-cancer treatment prior to 16-week assessment will be considered as not having achieved DCR at 16-week assessment.

(d) Overall Survival (OS)

OS is the time from date of first study treatment to the date of death from any cause. Patients who are alive or lost to follow-up at the time of the analysis will be censored at the last known alive date prior to the analysis data cut-off date.

(e) Duration of Response (DoR)

DoR is defined as the time from the first date of response (CR or PR) to first date of documented radiographical PD, per investigator using RECIST v1.1. This will only apply to patients with CR or PR. The censoring rules will be displayed in Section 3.2.1.

3.1.3 Other endpoints

Other secondary efficacy endpoint (CA19-9) is as stated within the protocol which will be detailed in in a separate document when applies.

3.1.4 Safety endpoints

Safety endpoints are adverse events, laboratory data including blood samples for determination of complete blood count, serum chemistry and urine or serum pregnancy test, vital signs, 12-lead electrocardiogram (ECG).

The Medical Dictionary for Regulatory Activities (MedDRA) version 20.1 or higher will be used to code the AEs. Toxicity will be graded according to the NCI CTCAE version 4.03.

3.1.4.1 Adverse events

An adverse event is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign, including abnormal laboratory findings, symptoms, or diseases temporally associated with the use of study regimen, whether or not considered related to study regimen. Worsening of a medical condition for which the efficacy of the study treatment is being evaluated will not be considered an adverse event.

(a) Treatment-emergent adverse event (TEAE)

An Adverse event will be considered as a TEAE if it begins on or after study treatment dosing or starts prior to dosing and increases in severity after dosing. The period for treatment-emergent adverse events (TEAEs) and safety findings will be from the time of first study treatment administration to 30 days after the date of last study treatment administration. If an adverse event begins on the date of first study treatment administration with no time recorded, the event will be considered as treatment-emergent.

(b) Serious adverse event (SAE)

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Other important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

(c) Severity of adverse event

Each adverse event will be graded according to the NCI CTCAE Version 4.03, which may be found at http://ctep.cancer.gov/reporting/ctc.html. For events not listed in the CTCAE, severity will be designated as mild, moderate, severe or life threatening or fatal which correspond to Grades 1, 2, 3, 4 and 5, respectively on the NCI CTCAE version 4.03 and higher, with the following definitions:

- **Mild**: an event not resulting in disability or incapacity and which resolves without intervention;

- **Moderate**: an event not resulting in disability or incapacity but which requires intervention;
- **Severe**: an event resulting in temporary disability or incapacity and which requires intervention;
- **Life-threatening**: an event in which the patient was at risk of death at the time of the event;
- **Fatal**: an event that results in the death of the patient.

(d) Relatedness of adverse event

The Investigator must attempt to determine if there exists reasonable possibility that an adverse event is related to the use of the study treatment. This relationship should be described as related or non-related.

(e) Dose limiting toxicities (DLTs)

DLTs will be assessed during the safety evaluation period (i.e. 28 days in Cycle 1; or 14 days after the 2nd dose of study treatment if there is a treatment delay according to the Study Protocol Amendment v7.0 Section 6.5) and documented in CRF. A summary of dose-limiting toxicity events documented will be provided.

3.1.4.2 Laboratory variables

Laboratory data will be collected throughout the study, from screening to the follow-up visits as per Schedule of Assessments for each cohort described in the Study Protocol Amendment v7.0.

(a) Complete blood count (CBC)

A complete blood count (locally and centrally assessed) will include a white blood count (WBC) and differential, hemoglobin, hematocrit and platelet count.

(b) Serum chemistry

Serum chemistry will include electrolytes (sodium, potassium, chloride and bicarbonate), BUN, serum creatinine, glucose, direct and total bilirubin, AST, ALT, alkaline phosphatase, lactate dehydrogenase (LDH), uric acid, total protein, albumin, calcium, magnesium and phosphate.

(c) Urine or serum pregnancy

A urine or serum pregnancy test will be obtained for all females of childbearing potential at screening, at the start of each cycle during study treatment, and at the End of Treatment (EoT) visit. Exempt female patients will include those who have undergone a bilateral oophorectomy or hysterectomy or who are menopausal (defined as absence of a menstrual cycle for at least 12 consecutive months).

(d) Other laboratory variables such as CA19-9 biomarker levels, UGT1A1*28, Biomarker samples and PK will be detailed in a separate document when applies.

3.1.4.3 Vital signs

Vital signs will include height (at screening only), weight, resting blood pressure, pulse, respiratory rate and temperature from screening to EoT visit.

3.1.4.4 Electrocardiogram (ECG)

A 12 lead ECG will include a description of the cardiac rate, rhythm, interval durations and an overall clinical interpretation. If the ECG is abnormal, abnormal not clinically significance or abnormal clinically significance should be indicated.

Electrocardiogram Abnormality Criteria

ECG Parameter[1]	Criterion[2]
Absolute QT or QTcF values (msecs)	> 450
	> 480
	> 500
Increase from baseline in QT or QTcF (msecs)	> 30
	> 60
Heart Rate (bpm)	> 100
Increase/decrease from baseline in Heart Rate (bpm)	> 30

[1]Fridericia (QTcF) corrections will be presented separately.

[2]Criteria were based on ICH E14 guidance except for heart rate.

3.1.5 Multiplicity

No multiple testing will be performed in this study.

3.1.6 Significance testing and estimation

No statistical test will be performed in this study.

3.2 Analysis methods

3.2.1 Efficacy

3.2.1.1 Primary efficacy analysis

The primary efficacy endpoint(s) is Progression-free survival (PFS).

PFS time will be determined as the time from the date of first study treatment to the first documented radiographical progression of disease (PD), per investigator using RECIST v1.1, or death from any cause, whichever comes first, in months and is calculated as follows:

$$\text{PFS} = \frac{\min(date\ of\ first\ documented\ radiographical\ PD,\ death) - date\ of\ first\ study\ treatment + 1}{30.4375}$$

PFS censoring rules are:

Condition	Date of Progression or Censoring	Event
No baseline tumor assessments	Date of the 1st treatment	Censored
Progression documented after new anti-cancer therapy	Date of the last non-PD tumor assessment prior to new anti-cancer therapy or Date of the 1st treatment if no post-treatment tumor assessment	Censored
Death documented after new anti-cancer therapy	Date of the last non-PD tumor assessment prior to new anti-cancer therapy or Date of the 1st treatment if no post-treatment tumor assessment	Censored
CCI		
Treatment discontinuation for clinical deterioration without documented progression or death	Date of the last non-PD tumor assessment or Date of the 1st treatment if no post-treatment tumor assessment	Censored
Treatment discontinuation for AEs or other reasons without documented progression or death	Date of the last non-PD tumor assessment or Date of the 1st treatment if no post-treatment tumor assessment	Censored

New anti-cancer therapy started prior to the treatment termination without documented progression	Date of the last non-PD assessment prior to starting new anti-cancer therapy or Date of the 1st treatment if no post-treatment tumor assessment	Censored
Patient still on treatment at time of analysis	Date of the last non-PD tumor assessment or Date of the 1st treatment if no post-treatment tumor assessment	Censored
None of the following: • documented progression • death • treatment termination • New anticancer therapy started • cancer-related surgery	Date of the last non-PD tumor assessment or Date of the 1st treatment if no post-treatment tumor assessment	Censored

PFS will be analyzed using Kaplan-Meier method and descriptively summarized at 3 months interval for each dose level cohort. Median PFS time and corresponding 95% confidence limits will be calculated based on Brookmeyer-Crowley method for each dose level cohort.

Figure displays

Kaplan-Meir curve of PFS will be plotted.

3.2.1.2 Secondary efficacy analysis

The secondary efficacy endpoints are as stated within the protocol:

(a) Best Overall Response (BOR)

BOR is defined as the best response as recorded from the start of study treatment until disease progression or start of new anti-cancer therapy. Patients without a post-baseline tumor assessment will be considered to be non-evaluable for BOR.

Categorisation of best overall response will be based on the RECIST v1.1 criteria using the following response categories: complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD) and not evaluable (NE). Note that SD should be assessed at least 6 weeks +/- 7days, i.e., at least 35 days (to allow for the assessment window) from enrolment.

(b) Overall Response Rate (ORR)

ORR is defined as the proportion of patients with a BOR characterized as either a Complete Response (CR) or Partial Response (PR) per RECIST v1.1 relative to the total number of evaluable patients.

Estimates of overall response rate and its corresponding 95% CI will be calculated using Clopper-Pearson method for each dose level cohort.

(c) Disease Control Rate at 16-week (DCR_{16}) assessment

A patient will be classified as having achieved disease control at 16-week assessment if the patient has not progressed at the 16-week assessment, i.e. has no PD up to and including the 16-week assessment with documented non-PD (SD, PR, or CR) assessment. Patients, who die, discontinue tumor assessments, or start new anti-cancer treatment prior to 16-week assessment will be considered as not having achieved DCR at 16-week assessment. Patients without a post-baseline tumor assessment will be considered to be non-evaluable for DCR even if they die, discontinue tumor assessments, or start new anti-cancer treatment prior to 16-week assessment.

For each treatment cohort, DCR_{16} is calculated as below:

$$DCR_{16} = \frac{number\ of\ patients\ who\ achieve\ disease\ control\ at\ 16\ weeks}{number\ of\ patients\ treated} * 100\%$$

Descriptive summary of Disease Control at 16-week assessment will be displayed in table for each dose level cohort. Estimation of DCR_{16} its corresponding 95% CI will be calculated based on Brookmeyer-Crowley method for each dose level cohort.

(d) Overall Survival (OS)

OS is the time from date of first study treatment to the date of death from any cause, in months and is calculated as follows:

$$OS = \frac{date\ of\ death\ or\ censoring - da\quad of\ first\ study\ treatment + 1}{30.4375}$$

Patients who are alive or lost to follow-up at the time of the analysis will be censored at the last known alive date prior to the analysis data cut-off date.

The last known alive date will be identified as the latest qualifying date from examination of the Overall Survival CRF form, laboratory sample dates, adverse event start and stop dates, concomitant medication start and stop dates as well as normal visit/follow-up dates. The censored Overall Survival time will be computed as (date last known to be alive - date of enrolled + 1).

Similar to PFS, OS will be analyzed using Kaplan-Meier method and descriptively summarized for each dose level cohort. Median OS time and corresponding 95% confidence limits will be calculated based on Brookmeyer-Crowley method for each dose level cohort.

Figure displays

Kaplan-Meir curve of OS will be plotted.

(e) Duration of Response

DoR is defined as the time from the first date of response (CR or PR) to first date of documented radiographical PD, per investigator using RECIST v1.1. This will only apply to patients with CR or PR and will be calculated as follows:

$$\text{DoR} = \frac{date\ of\ first\ PD\ or\ censoring - date\ of\ first\ response + 1}{30.4375}$$

If a patient is given a new anti-cancer therapy prior to first response, DoR will not be calculated.

Censoring will occur as follows:

- If a patient is known to be alive and progression-free, DoR will be censored on the date of the last tumor assessment
- If a patient is a given new anti-cancer therapy prior to PD and after first response, DoR will be censored on the date of the last progression-free tumor assessment prior to the start date of new anti-cancer therapy
- If a patient dies, DoR will be censored on the date of death.

Similar to PFS, DoR will be analyzed using Kaplan-Meier method and descriptively summarized for each dose level cohort.

3.2.1.3 Others

Data listing will be presented and sorted by cohort, patient ID and timepoint for CA19-9 per CRF.

3.2.2 Safety

Safety analyses (adverse events and laboratory analyses) will be based on safety population.

Laboratory data will be presented by cycle. Abnormal laboratory values will be assessed using all available data and toxicity grading will be assigned according to NCI CTCAE version 4.03 toxicity scale, where criteria are available to do so. Laboratory, vital signs, and ECG data will be summarized according to parameter type.

3.2.2.1 General considerations for safety assessment

- Unless otherwise stated, baseline will be defined as the last non-missing measurement prior to dosing with study treatment. 'End of Study (EoS)' is defined as the last available post-treatment assessment when subject finally ends participation in the trial. 'End of Treatment (EoT) Follow-up Visit' is defined as 30 days (+/- 14 days) post last dose of study treatment
- The time windows per the Schedule of Assessment should be exhaustive so that data recorded at any time point has the potential to be summarized. Inclusion within the time window should be based on the actual date and not the intended date of the visit
- Extra assessments (e.g. laboratory, vital signs, or ECG data associated with non-protocol clinical visits or obtained in the course of investigating or managing AEs) will be included in listings with flagged [U], but not summaries
- For visit-based summaries, if there is more than one value per patient within a time window then the value closest to the planned study day should be summarized. If there

is more than one closet value per patient then the last value by the chronological order should be summarized.

3.2.2.2 Adverse events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 20.1 or higher. Toxicity will be graded according to the NCI CTCAE version 4.03. Adverse events will be tabularized by each dose level cohort. AE will be summarized by System Organ Class and preferred term. All adverse event data will be listed by patient.

General Rules for summarizing AEs:

(1) An AE will be considered as treatment-emergent AE (TEAE) if it begins on or after study treatment dosing or starts prior to dosing and increases in severity after dosing. In case of missing dates, an AE will be considered as treatment-emergent (See Section 3.1.4.1a)).

(2) In the event of multiple adverse events being reported by the same subject, the most serious causality (related > not related) will be chosen.

(3) In the event of multiple occurrences of the same adverse events being reported by the same subject, the maximum intensity (Grade 5 > Grade 4 > Grade 3 > Grade 2 > Grade 1 > missing > not applicable) and the most serious causality (related) will be chosen.

(4) If a subject experience the same AE (i.e. same preferred term) more than once, they are only counted once under the count for preferred term.

(5) If a subject experiences more than one AE in a particular system organ class, they will only be included once in the count for the system organ class, but will appear in the count for each appropriate preferred term within the system organ class (unless it is the same preferred term).

(6) AEs related to study treatment include those AEs with a relationship to any of the 4 study drugs of 'related' or if there is a missing relationship in any of the 4 study drugs on the AE page of the CRF.

(7) AEs leading to dose discontinuation include those AEs with dose discontinuation of any of the 4 study drugs on the AE page of the CRF.

(8) AEs leading to dose adjustment include those AEs with dose adjustment (infusion delayed, infusion interrupted, infusion stopped, and dose decreased) of any of the 4 study drugs on the AE page of the CRF.

(9) For AE severity the following rules will be applied in determining the counts of AEs:

- An individual subject who experiences two AEs of the same preferred term of the same severity will be included once in the appropriate severity count for the particular AE
- An individual subject who experiences two AEs of the same preferred term but different severity will be included once in the severity count for the higher severity but not in the count for the lesser severity
- In the total counts for each severity classification, an individual subject who experiences two AEs of different preferred term of the same severity will be included once in the total for the appropriate severity

- In the total counts for each severity classification, an individual subject who experiences two AEs of different preferred term of different severities will be included once in the total for each of the appropriate severities.

Tabular summaries will be presented for each dose level cohort and combined selected dose level cohort. The following summaries will be reported for AEs, TEAE regardless of study treatment relationship, TEAE possibly related to study treatment, TEAE grade 3 and above regardless of drug relationship, TEAE grade 3 and above possibly related to study treatment, serious AEs (SAEs), AE leading to dose discontinuation, dose adjustment, and AE leading to death:

- Overall summary of adverse events will descriptively summarize all adverse events, treatment-emergent adverse events (TEAE), serious adverse events (SAEs), adverse events leading to infusion delayed, infusion interrupted, infusion stopped, study treatment discontinued, TEAE-related to study treatment TEAE Grade 3 and above
- Summary of AE by system organ class (SOC) and preferred term (PT) by alphabet order
- Summary of AE (AE, TEAE, SAE) and Dose-limiting Toxicity by system organ class (SOC) and preferred term (PT) and by decreasing frequency
- Summary of the number and percentage of patients reporting an AE (TEAE) by severity, SOC and PT, by decreasing frequency
- Summary of the number and percentage of patients reporting a treatment-related AE (TEAE, SAE, Grade 3 and above TEAE) by SOC and PT, by decreasing frequency
- Summary of the number and percentage of patients reporting a treatment-related TEAE by CTCAE grade, SOC and PT, by decreasing frequency
- Summary of the number and percentage of patients reporting a grade 3 and above AE (TEAE) by SOC and PT, by decreasing frequency
- Summary of the number and percentage of patient reporting TEAEs leading to dose discontinuation and dose adjustment (infusion delayed, infusion interrupted, infusion stopped, and dose decreased) by SOC and PT, by decreasing frequency
- Summary of the number and percentage of patient reporting TEAEs leading to death by SOC and PT, by decreasing frequency
- Summary of the number and percentage of patient reporting treatment-related TEAEs leading to death by SOC and PT, by decreasing frequency.

Listings of all AEs /SAEs/AEs leading to dose discontinuation will be presented in each dose level cohort and sorted by subject id, primary system organ class, preferred term and verbatim text for all adverse events recorded during the study, onset day relative to the first treatment date of AEs, date of Resolution, DLT AEs, SAEs, related to study treatment.

Listing of death will be presented in each dose level cohort.

Treatment Emergent Adverse Events (TEAE) will be flagged (*) in the adverse events listing.

3.2.2.3 Summary of DLT for Nal-IRI + 5-FU/LV + Oxaliplatin

Dose-limiting toxicity events will be summarized for each dose level cohort and combined selected dose level cohort.

A listing of dose-limiting toxicity event will be presented and sorted by cohort, patient id, primary system organ class, preferred term and verbatim text.

3.2.2.4 Laboratory data

Scheduled clinical safety laboratory parameters will be summarized. Summary tables will include descriptive statistics for original values and change from baseline by cycle and/or by each scheduled visit for each dose level cohort.

Shift tables of baseline value CTCAE grade to worst value CTCAE grade and last value CTCAE grade will be presented for each dose level cohort.

Abnormal lab values will be classified as low (lower than normal limit), normal (within normal range) and high (> upper normal limit). Laboratory values will also be assessed according to NCI CTCAE Version 4.03 grades, where possible. Abnormal lab values will be flagged (Low [L], High, [H], abnormal clinically significant [C],) where applicable in the listing. Any unscheduled laboratory assessments will be flagged [U] in the listing.

In addition, a separate listing will be created for all grade 3 and higher post-baseline laboratory observations.

Graphic displays will also be produced. Summary graphs showing boxplots (showing minimum, 1st quartile, median, 3rd quartile, maximum) for each dose level cohorts over time will be produced. Corresponding normal range limits will be indicated on the figures.

The following clinical parameters will be summarized:

Test Category	Laboratory Parameters
CBC with platelet and differentials	Basophils, Eosinophils, Hematocrit, Hemoglobin, Lymphocytes, Monocytes, Neutrophils, Platelet count, WBC count
Serum Chemistry	Albumin, Alkaline Phosphatase (ALP), ALT (SGPT), AST (SGOT), Bicarbonate, Calcium, Corrected Calcium, Chloride, Glucose, Lactate Dehydrogenase (LDH), Magnesium, Phosphate, Potassium, Serum Creatinine, Sodium, Total Bilirubin, Direct Bilirubin, Total Protein, Urea Nitrogen (BUN), Uric Acid

Other laboratory tests in CRF will be listed in listing by dose level cohort including UGT1A128, CA19-9, PK sample collection. The analysis plan for biomarker and PK parameters will be detailed in separate document when applies.

3.2.2.5 Vital signs

Descriptive summaries of actual values and changes from baseline will be calculated for vital signs. Vital signs will include height (at screening only) (cm/in), weight (kg/lb), resting blood pressure (mmHg), pulse (beats/min), respiratory rate (breaths/min) and temperature (C/F) by dose level cohort and scheduled visit.

Where vitals sign assessments are taken in multiple for a single visit, the value closest to the scheduled visit will be selected and used in summaries and all observations will be presented in listings. If there is more than one closet value per patient then the last value by the chronological order will be selected. Baseline values will be defined as the last vital signs measurement collected prior to the first dose of study treatment.

Vital signs, both observations and change from baseline, will be listed at each assessment by subject. Any unscheduled vital signs will be flagged [U] in the listing.

3.2.2.6 ECG

Descriptive summaries of actual values and changes from baseline will be presented by cycle for ECG parameters [heart rate, RR interval, PR interval, QRS interval, QT (uncorrected) interval and QTcF (Fridericia's correction: QTcF=QT/(RR)^1/3) interval]. RR interval will be calculated as $(QT/QTcF)^3$. A separate display will be provided which summarizes the change from baseline to the most extreme high or low value at any time during treatment.

Additional summaries will be produced for ECG data. The number and percentage of subjects exceeding the thresholds at each visit will be shown for HR and QTcF values separately. The abnormal ranges to be used are:

- HR (> 100)
- QTcF (>450, > 480, > 500).

A summary of the number and percentage of subjects with QT and QTc change from baseline values exceeding thresholds at each visit will be shown for HR and QTcF values separately.

The abnormal ranges to be used are:

- HR (> 30 increase/decrease from baseline)
- QTcF (>30, > 60 increase from baseline).

For heart rate, RR interval, PR interval, QRS interval, QT interval and QTcF interval, baseline is defined as the average of two independent readings on the last visit of ECG measurement collected prior to the first dose of study treatment. For rhythm and ECG interpretation, baseline is defined as the last finding prior to the first dose of study treatment. For continuous ECG parameters, summary statistics will be presented at each scheduled assessment for actual values and changes from baseline. The summary of normal, abnormal not clinically significance or abnormal clinically significance ECG will be displayed. ECG results, both observations and change from baseline, will be listed at each assessment subject. Any unscheduled ECG will be flagged [U] in the listings.

3.2.3 Missing data and outliers

3.2.3.1 Missing data

Missing data will not be imputed, unless otherwise stated. When applies, missing data category will be included in categorical data summary and will be summarized by dose level cohort and timepoint using counts and percentages.

3.2.3.2 Missing or incomplete dates

In all listings, missing or incomplete dates should be left as they have been recorded. However, for calculation / sorting / assignation based on dates, the following methods will be used:

- In any partial AE start dates, if year and month are available:
  1) If available years and months are prior to first study treatment years and months, the analyses dates will be derived as first day of the month or first study treatment start date, whichever comes first.
  2) If available years and months are after first study treatment years and months, the analyses dates will be derived as first day of the month or first study treatment start date, whichever comes first.
  3) If available years and months equal to first study treatment years and months, the analyses date will be derived as first study treatment start date or AE end date, whichever comes first.

  If only year is available:
  1) If available years are prior to first study treatment years, the analyses dates will be derived as first day of January or first study treatment start date, whichever comes first.
  2) If available years are after first study treatment years, the analyses dates will be derived as first day of January or first study treatment start date, whichever comes first.
  3) If available years equal to first study treatment dates, the analyses dates will be derived as first study treatment start date or AE end date, whichever comes first.

  If AE start dates are completely missing, the analyses dates will be derived as first study treatment start date or AE end date, whichever comes first.
- In any partial AE end dates, if years and months are available, the analyses dates will be derived as last day of the month. If only years are available, the analyses dates will be derived as 31st of December.
- In any other partial start dates, if years and months are available, the analyses dates will be derived as first day of the month. If only years are available, the analyses dates will be derived as first day of January.
- In any other partial end dates, if years and months are available, the analyses dates will be derived as last day of the month. If only years are available, the analyses dates will be derived as 31st of December.
- The most conservative approach will be systematically considered (i.e. if the onset date of an AE/concomitant medication is missing / incomplete, it is assumed to have occurred during the study treatment phase (i.e. a TEAE for AEs) except if the partial onset date or other data [stop date, …] indicates differently).
- A missing/incomplete date of medical history or disease diagnosis will be assumed to have occurred before any study treatment.

If a partial date and the associated information do not allow to state about the assignation to a category, all the possible categories will be considered (i.e. an AE could be assigned to several possible doses at event onset according to its partial onset date and stop date. Particularly an AE with missing start date will be assigned to each dose received before its end date. Similarly, a medication with partial start and stop dates could be considered as prior and concomitant treatment).

3.2.3.3 Outliers

All statistical analysis should be performed with the actual values.

3.2.4 Subject disposition

Disposition of patients will be summarized at each dose level cohort and combined selected dose level cohort including patients enrolled, treated, and discontinued of study and discontinued of treatment. Reasons for discontinuation of study and treatment will be tabulated.

Reasons for discontinuation of study are subject deceased, subject withdrew consent from follow-up, subject is lost to follow-up, sponsor decision, significant noncompliance with the protocol, investigator decision, use of prohibited concomitant medications, and other.

Reasons for treatment termination are progressive disease based on RECIST v1.1 criteria, radiologically determined progressive disease per RECIST v1.1, symptomatic deterioration, clinical deterioration, sufficient to prevent further radiological assessment, adverse event, protocol violation/non-compliance, subject deceased, investigator decision, sponsor decision, subject is lost to follow-up, subject became ineligible post randomization but prior to dosing, pregnancy, and other.

Percentages of subjects will be based on the number of subjects enrolled as 100%.

In addition, by-subject listing will be provided for subjects who discontinued the study early with reason for discontinuation at each dose level cohort.

3.2.5 Study treatment exposure/Compliance

Oxaliplatin, nal-IRI, 5-FU and leucovorin will be administered at dose levels as indicated in Table 1 on Days 1 and 15 of each 28-day cycle. For each patient in each cycle on Day 1 or 15, the expected dose and actual dose of Oxaliplatin, nal-IRI, 5-FU and leucovorin administered were calculated and recorded in CRF. Oxaliplatin, nal-IRI, 5-FU and leucovorin can be calculated as:

Total # of completed cycles received medication by cohort = sum of completed cycle # received medication. The completed cycle # receive medication is the cycle consists of D1 and D15 received medication.

Total expected dose for cycle # = {intended total calculated dose on day 1 + intended total calculated dose on day 15} for cycle #. Total cumulative expected dose is sum of total expected dose from cycle 1 to the last cycle.

Total actual dose for cycle # = {actual dose administered on day 1 + actual dose administered on day 15} for cycle #. Total cumulative actual dose is sum of all total actual dose from cycle 1 to the last cycle.

Compliance for cycle # (%) = Total actual dose for cycle # / Total expected dose for cycle # * 100%.

Overall compliance (%) = Total cumulative actual dose / Total cumulative expected dose) * 100%.

Time on treatment: number of days from first treatment to last treatment:

Time on treatment = {date of last exposure - date of first exposure} + 1.

Dose intensity (DI): percent of the total weekly intended dose delivered to a patient per week of treatment:

% of DI =100*{actual DI} / {planned DI};

where

actual DI = {cumulative actual dose in mg/m^2} / {actual duration of exposure DI/7} mg/m^2/week

and

planned DI = {cumulative planned dose in mg/m^2} / {planned duration of exposure DI/7} mg/m^2/week

and

actual dose (mg/m^2) = actual dose (mg) / Body Surface Area (m^2)

and

actual duration of exposure DI = {date of last dose + planned days to next dose} - {date of first dose}+1

and

planned duration of exposure DI = Number of cycles with non-missing planned dose×28 (A complete cycle is planned doses at both day 1 and day 15. A half cycle is planned dose at either day 1 or day 15.)

To convert actual dose from mg to mg/m^2, the following methods will be used when Body Surface Area (BSA) is missing:

- If BSA is missing, but weight and height is available, BSA will be derived from weight and height (Appendix 1)
- If BSA is missing on either Day 1 or 15 within the cycle, the available BSA in the same cycle will be used to impute the missing BSA. If BSA is missing on both Day 1 and 15 within the cycle, the latest available BSA prior to the cycle will be used to impute the missing BSA.

Time to first dose reduction, delayed, interrupted (months) will be calculated by {date of first dose reduction - date of first administration of study treatment + 1} / 30.4375.

Study exposure will be summarized using descriptive statistics separately for each cohort. Total cumulative expected and actual and compliance for Oxaliplatin, nal-IRI, 5-FU and leucovorin dose (mg) for each patient will be summarized using descriptive statistics. Frequency counts of patient with Oxaliplatin, nal-IRI, 5-FU and leucovorin will also be summarized. Summary of

exposure adjustment (reduced, delayed, interrupted) will be displayed. The supportive listing provides data collected on the (Oxaliplatin, nal-IRI, 5-FU and leucovorin) Administration CRF pages for each patient.

3.2.6 Demographic and baseline characteristics

Demographic and baseline characteristics data that will be summarized at each dose level cohort include age (<65; ≥65), gender, race, ethnicity, weight (<70, ≥70 – ≤90, >90) and height collected at Screening Visit, Body Mass Index (BMI) (normal (<25), overweight (25-30), obese (>30)), Body Surface Area (BSA) calculated using weight and height from Screening Visit, detailed in Appendix 1. By-subject listing of subjects demographic and other baseline characteristics data will be provided at each dose level cohort.

Categorical variables will be summarized by frequency distributions (number and percentage of patients) and continuous variables will be summarized by descriptive statistics (mean, standard deviation, median, minimum, and maximum).

Eastern Cooperative Oncology Group (ECOG) performance status (i.e. ECOG performance score of 0 or 1) and Karnofsky Performance Status (KPS) with score 100 or 90 or 80 or 70 or 60 or ≤50 will be listed and summarized at each dose level cohort.

3.2.7 Medical history

Prior medical and surgical procedures and chemotherapies collected in CRF will be coded using the latest version of MedDRA 20.1 or higher. For each dose level cohort, medical history will be summarized by system organ class (SOC) and preferred term (PT). Listing will be sorted by dose level cohort, organ class system, subject identification number and preferred term.

Other prior medical and surgical procedures and chemotherapies in CRF will be listed in listing by dose level cohort.

3.2.8 Protocol deviations

All the protocol deviations identified in the Protocol Deviation Specification prior to database lock will be summarized by Major / Minor and listed by subject. Protocol deviation criteria and its impact on statistical analysis population will be documented in a separate document.

3.2.9 Prior and concomitant therapies

Prior and concomitant medications are defined as follows:

- Prior medications that start and stop prior to the date of first treatment administration.
- Concomitant medications are medications start on or after the date of first treatment administration.
- Prior and Concomitant medications are medications start before the date of first treatment administration and stops on or after the date of first treatment administration.

Concomitant medication will be summarized using frequency tables by Anatomical therapeutic chemical (ATC) classification code based on World Health Organization Drug Dictionary

(WHODD) SEP 2017 or later. All details recorded in relation to prior and concomitant medication and procedure will be listed by subject at each dose level cohort.

3.2.10 Pharmacokinetics

Analysis of pharmacokinetics will be detailed in a separate document when applies.

A listing of PK sampling time and results will be provided.

3.2.11 Derived data

The derived data are variables which are calculated from the raw data in the CRF and not included in the EDC database. The derivation rules and algorithms will be detailed in a separated document (Analysis Datasets (ADs) Specification).

3.2.12 Visit windows

All data will be organised and analysed according to Schedule of Assessments outlined in Appendix 2 in SAP.

3.2.13 Rules and data formats

The following general principles will be followed throughout the study:

- All analyse and summaries will be performed and presented separately for each cohort.
- Categorical variables will be summarized in terms of the number of subjects providing data at the relevant time point (n), frequency counts and percentages for each category, unless otherwise stated.
- Continuous variables will be summarized in terms of the mean, standard deviation median, minimum, maximum and number of observations, unless otherwise stated.
- The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean and median will be reported to one more decimal place than the raw data recorded in the database. The standard deviation will be reported to two more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistic.
- Unless otherwise stated, percentages will be calculated using a denominator of all subjects in a specified population. The percentages will be presented to one decimal place and 0% will not be presented. The denominator will be specified in a footnote to the tables for clarification if necessary.
- All text fields must be left justified and numeric or numeric with some text specification (e.g.: not done, unknown, <4.5, …) must be decimal justified. Dates will be presented in the format [ddmmmyyyy] and times in the format [hh:mm].
- Statistical software SAS for Windows Version 9.3 or higher (SAS Institute, Inc., Cary, NC) will be used for all analyses.

3.2.14 Pooling of centres

Subject from all centres will be pooled for all analyses. Subgroup analysis on individual or groups of centres is not planned.

3.2.15 Interim analysis

No interim analysis will be performed.

3.2.16 Role of independent data monitoring committee (DMC)/interim data review committee

No independent data monitoring committee/interim data review committee will be used in this study. However a DLT Committee (comprising the Investigators, the Medical Monitor, and the Sponsor) will review all available data (DLT, SAE, and grade 3-4 adverse events, any available pharmacokinetic, pharmacogenomic, pharmacodynamic results and any initial efficacy data) at the completion of the safety evaluation period for dose level cohorts -1 to -3 (Part 1A) detailed in the Table 1.

4 COMPUTER SYSTEMS, SOFTWARE AND VALIDATION OF PROGRAMS

4.1 Software

All tables, listings and figures will be produced and statistical analysis performed using SAS® version 9.3 or higher. All outputs will be in PDF Format.

4.2 Validation programs

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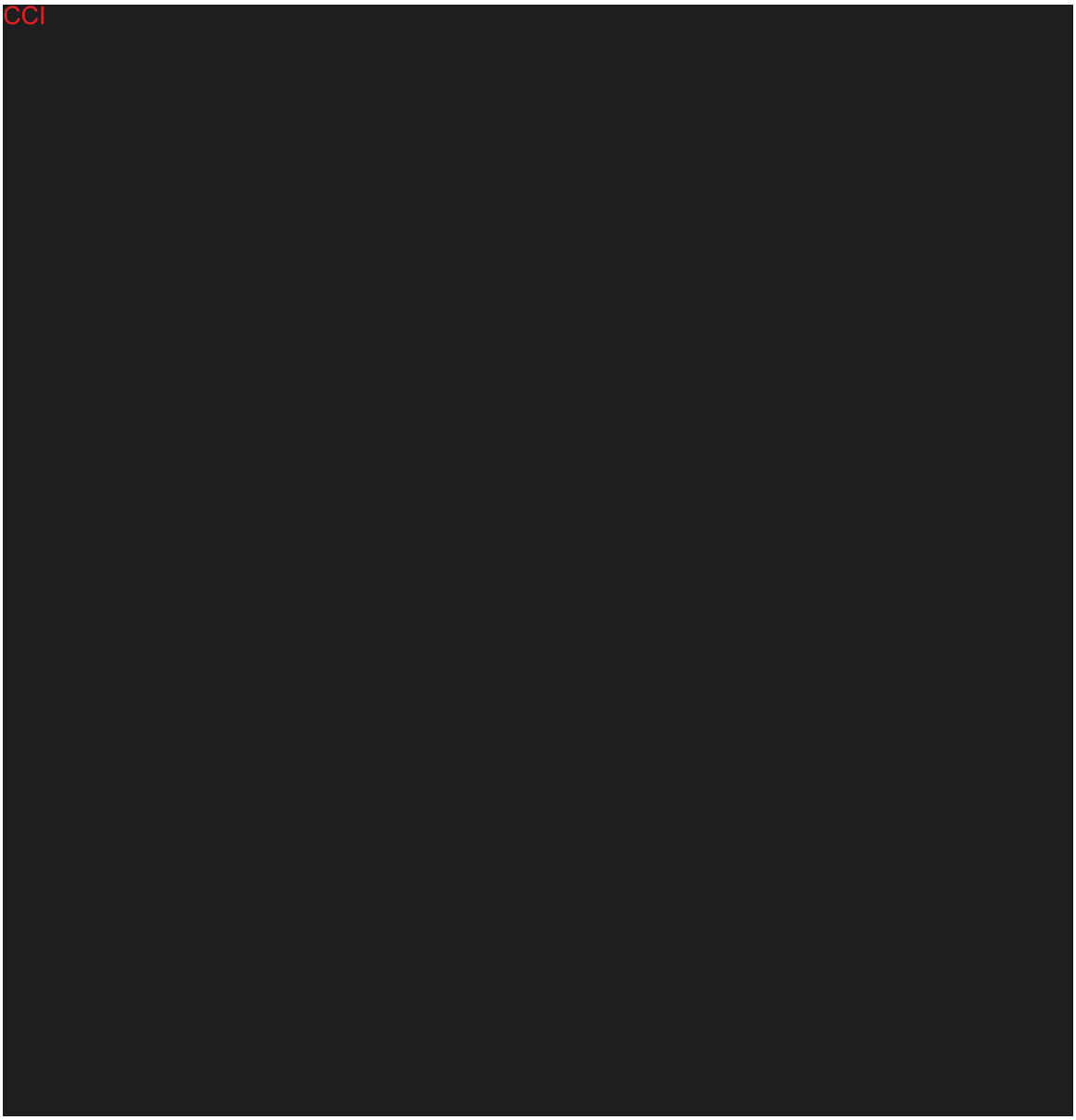

4.3 Restitution of the programs

All programs (including Macros and analysis datasets) producing the tables, listings and statistical output along with associated logs should be given to the sponsor when the tables, listings, figures and statistical analysis has been finalised.

5 CHANGES FROM PROTOCOL

No changes affecting the statistical analysis defined in the protocol & protocol amendments.

6 REFERENCES

(1) Guidelines for Industry: E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs, International Conference on

Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, October 2005.

(2) Guidelines for Industry: Structure and Content of Clinical Study Reports (E3), International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, July 1996.

(3) Clopper, C. and Pearson, E. S. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika. 1934. 26: 404–413.

(4) Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009. 45:228-247.

(5) Hall, W. J. and Wellner, J. A. Confidence Bands for a Survival Curve from Censored Data. Biometrika. 1980. 67:133–143.

(6) Kaplan, E. L. and Meier, P. Nonparametric Estimation from Incomplete Observations, Journal of the American Statistical Association. 1958. 53:457–481.

7 APPENDICES

Appendix 1: Derived Data

The following derived data will be calculated and included in the listings:

1) **Age (specified DEMOG table)**
   Subject age (years) will be derived as (screening date – birth date)/365.25 and truncated to the largest integer that is less than or equal to the calculated result.

2) **BMI (specified VSIGN table)**
   BMI (kg/m^2) will be derived as Weight (kg)/[Height(cm)/100]^2 and rounded to the nearest decimal.

3) **Body Surface Area (specified VSIGN table)**
   Body Surface Area (m^2) will be derived as (Weight (kg)$^{0.425}$ * Height(cm)$^{0.725}$ * 71.84)/10000 and rounded to the nearest decimal.

4) **Changes from baseline**
   Changes from baseline will be calculated as a difference from baseline (e.g. assessment at the visit – assessment at baseline).

5) **Adverse event duration**
   If the start and end dates of the adverse event are identical, then "<1" day will be presented. If the start date or the end date is partial, the duration will be presented as "≥2". If the start date or end date is missing, the duration will be missing.

6) **Days since last dose for study treatment administration or discontinued subject**
   The days since last dose for study treatment administration will be calculated as (study treatment administration date/time - previous administration date/time) + 1 and presented in days hh:mm. The days since last dose for discontinued subject will be calculated as (discontinued date - last administration date) + 1 and presented in days.

7) **Study exposure**
   Study exposure in days will be calculated as (last visit attended - screening date) + 1.

8) **Study day**
   Study day will be defined as '-1' for the day prior to treatment and as '1' for the day of treatment (i.e. day 0 does not exist).

9) **The cumulative dose is the sum of all doses from cycle 1 up to last cycle.**

10) **Duration of Study Treatment Exposure**
    Duration (days) = (last dose or infusion date-first dose or infusion date +1) + **13** days.

11) **Corrected Calcium**
    Corrected calcium (mmol/L) = serum calcium (mmol/L) + 0.025 * (40 - serum albumin (g/L))

Appendix 2: Schedule of Assessments

Procedure	Screening Phase	Treatment Phase								Follow Up Phase	
	-28d	Cycle 1[19]				Additional Cycles[19]			Every 8w after 1st dose	End of Treatment Visit[18]	Every 2 months from EoT Follow-up visit
		D1	D3	D8	D15	D1	D8	D15			
Informed consent	X										
Medical history	X[1]										
Demographics	X[1]										
Vital signs	X[2]	X		X	X	X		X		X	
ECOG PS	XX[2, 23]	X				X				X	
KPS PS	XX[2, 24]										
CBC[4]	X[2]	X		X	X	X	X	X		X	
Serum chemistry[4,]	X[2, 25]	X		X	X	X		X		X	
CA19-9	X[2]								X[17]	X[20]	
UGT1A1*28	X[2, 5]										
Pregnancy test	X[2]	X				X				X	
ECG[6]	X[1,7]									X	
Archived slides[8]	X										
Plasma for PK[10]		X[9]	X[10]	X[11]	X[12]					X[26]	
Biomarker analysis[12, 13]		X[15]				X				X	
Concomitant meds and procedures	X[1]	X	X	X	X	X	X	X		X	
Dosing[16]		X			X	X		X			
AE / Hospitalization assessment & reporting	X[15]	X	X	X	X	X	X	X		X	
Disease evaluation[16]	X[1]								X[17]	X[18]	X[21]
Overall Survival											X[22]

[1] Procedures to be completed within 28 days of 1st dose of study treatment
[2] Procedures to be completed within 7 days of 1st dose of study treatment
[3] HRQL questionnaires must be completed before study treatment administration
[4] After screening, samples should be obtained within 2 days from scheduled date of collection
[5] Result not required prior to enrollment in the study or prior to receiving the initial dose of nal-IRI.
[6] To be repeated as clinically indicated during the study
[7] Two independent readings at least 1 minute apart

[8] Collection of archived tumor block or paraffin embedded slides is required, if available
[9] Samples collected at the following timepoints: pre-dose (within 24 hours prior to nal-IRI infusion); at the end of the nal-IRI infusion (+30 mins) and at the end of the oxaliplatin infusion (+5 mins)..
[10] Sample collected within 2 hours prior to the completion of the 5-FU infusion.
[11] Sample collected +168 hours/7 days after the completion of the nal-IRI infusion (±24 hours).
[12] Sample collected just prior to dosing with nal-IRI (within 24 hours).
[13] Blood will be collected for biomarker analyses: plasma samples will be collected at all timepoints; additionally, whole blood and serum samples will be collected on Cycle 1 Day 1 only
[14] Study treatment administration should occur ±2 days from scheduled date of administration
[15] Adverse events that occur during screening should be documented as pre-existing conditions; only SAEs that are felt by the Investigator to be directly related to a study procedure should be reported during screening.
[16] Disease evaluation according to RECIST v. 1.1 (see in the Study Protocol Amendment V5.0 Section 7.2.6)
[17] Disease evaluations and CA19-9 should be done every 8 weeks (± 7 days) after 1st dose
[18] Unless completed in the prior 8 weeks
[19] All cycles are 28-day cycles, unless modified due to toxicity
[20] The End of Treatment (EoT) Follow-Up visit should occur 30 days (± 14 days) after last dose
[21] For patients who discontinue the study for reasons other than radiologically confirmed disease progression only (e.g. patients who are removed due to adverse events), imaging studies should be continued until documented progression of disease per RECIST v1.1 (see in the Study Protocol Amendment V5.0 Section 7.2.6).
[22] Follow-up contacts should be made every 8 weeks (± 7 days) until death or study completion; data collected should include overall survival status as well as subsequent treatment information.
[23] ECOG to be performed at Screening, and within 72 hours prior to first dose if first dose occurs more than 72 hours post screening. ECOG assessment requires determination by two independent assessors. In the case of a discrepancy between the 2 assessments, the one with a lower score will be selected at each assessment.
[24] KPS to be performed at Screening and within 72 hours of enrollment/randomization. KPS assessment requires determination by two independent assessors. In the case of a discrepancy between the 2 assessments, the one with a lower score will be selected.
[25] Serum albumin needs to be collected at Screening Visit and within 72 hours prior to enrolment/ randomization to confirm exclusion criteria p (both labs at screening and prior to enrolment/randomization may be confirmed locally) (in the Study Protocol Amendment V5.0 Section 5.2).
[26] Sample to be collected within 5 minutes after ECG recording.

CCI Electronic Signature Page

This page is the manifestation of the electronic signature(s) used in compliance with CCI International's electronic signature policies and procedures and in compliance with applicable regulations.

UserName: PPD
Title: PPD
Date: Tuesday, 18 May 2021, 09:31 PM GMT Standard Time
Meaning: Document contents approved.
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