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# STATISTICAL ANALYSIS PLAN

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| **Protocol Title:** | An open-label, randomised, multicentre, phase III study of irinotecan liposome injection, oxaliplatin, 5-fluorouracil/leucovorin versus nab-paclitaxel plus gemcitabine in subjects who have not previously received chemotherapy for metastatic adenocarcinoma of the pancreas |
| **Protocol Number:** | D-US-60010-001 |
| **Protocol Version/Date:** | Version 5.0/19 August 2021 |
| **Investigational Product:** | Irinotecan liposome injection (IPN60010) |
| **Sponsor:** | Ipsen Bioscience<br>Ipsen Group<br>1 Main St, Cambridge, MA 02142, USA |
| **SAP Version/Date:** | Version 5.0/20 September 2022 |

**CONFIDENTIAL**

# SIGNATURE PAGE

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| **Protocol Number:** | Version 5.0 |
| **SAP Version/Date:** | Version 5.0/20 September 2022 |

We, the undersigned, have reviewed and approved this Statistical Analysis Plan:

| **Signature** | **Date** |
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# VERSION HISTORY

| Version | Version Date | Description |
|---|---|---|
| 1.0 | 16 January 2020 | Original signed version |
| 2.0 | 16 September 2020 | Updates based on protocol version 4.0<br>• Futility-only interim analysis changes to at 181 OS events; interim analysis for both futility and efficacy at 401 overall survival events; total sample size changes to 565 overall survival events.<br>• Other updates to be consistent with protocol version 4.0. |
| 3.0 | 06 January 2022 | • Futility-only interim analysis at 181 OS event is removed. The interim analysis is planned when at least 272 OS events. Final analysis is planned at least 543 OS events.<br>• Move study endpoint description and derivation language in section 2 to analysis section 3 and appendix.<br>• Adverse events of special interest language is modified to use case report option. Standard MedDRA Query for adverse events of special interest is removed from appendix.<br>• Duration of response definition is modified to include death in addition to tumor progression using RECIST 1.1.<br>• BOR definition is clarified from randomization until documented objective disease progression using RECIST Version 1.1.<br>• Estimand language is added in section 3.4.<br>• Other editorial revisions throughout the statistical analysis plan document.<br>• Other updates to be consistent with protocol version 5.0.<br>• Clarify further subsequent anti-cancer therapy includes drug therapy, curative radiotherapy, curative surgery |
| 4.0 | 10 August 2022 | • Change time to deterioration exploratory objective only includes GHS, function domains, and disease related symptoms from EORTC QLQ-C30<br>• Change analysis day calculation from using first dose of study treatment to randomization.<br>• Disposition includes subjects who received non-planned study treatments and subjects with ongoing long-term follow up<br>• Remove summary of post-treatment medications<br>• Modify prior medication definition |

| Version | Version Date | Description |
|---|---|---|
| | | • Change OS sensitivity analysis Wilcoxon analysis to Unstratified log rank<br>• Add Unstratified log rank to PFS sensitivity analysis<br>• Remove summary and plots for tumor size (sum of diameters)<br>• Add analysis visit windows for PRO data<br>• Clarify new anti-cancer therapy to subsequent anti-cancer therapy (drug therapy, curative radiotherapy, curative surgery) including new antineoplastic treatment.<br>• Clarify analysis Intent-to-Treat definition from all randomised subjects who have given their informed consent to all randomised subjects to whom study treatment has been assigned by randomization. Subjects will be analyzed according to the assigned treatment per randomization procedure.<br>• Clarify Safety Population is a subset of the ITT population that received at least one dose (including a partial dose) of any component of the study medication in the combination therapy). Subjects will be analyzed according to the actual received treatment<br>• Tumor assessments performed after or on any further subsequent anti-cancer therapy will not be used in the assessment of best overall response (BOR).<br>• Clarify TEAEs leading to discontinuation of study treatment summary will also include related to IMP and related to Irinotecan liposome injection<br>• Sensitivity analysis of OS using Cox regression with stepwise selection and univariate analysis of OS for prognostic factors are removed.<br>• Change all baseline summaries to use ITT population<br>• Add AE combining rules and modify TEAE summaries<br>• Add lab abnormality tables<br>• Change analyses of QoL primarily based on ITT population. PRO population may be used as the sensitivity analyses<br>• Add results from unstratified log-rank test and Cox model into main OS and PFS analyses<br>• Clarify study exposure analyses<br>• Update TEAE and death summary |

| Version | Version Date | Description |
|---|---|---|
| **5.0** | 20 September 2022 | • Clarification of ECOG baseline definition in section 3.1.3<br>• Update demographic and baseline characteristics in section 3.3.4<br>• Section 3.3.8 add withdrawal of study consent with lost to follow-up to last date of exposure of study drug calculation<br>• Remove withdrawal from study ICE from Table 1 in section 3.4.1<br>• PFS censoring rules in section 3.4.2 Table 3 replace censoring rule of treatment discontinuation with withdrawal of study consent and/or lost to follow-up<br>• PFS sensitivity analysis and Table 4 in section 3.4.2 update following Table 3 change<br>• clarify ICE1 handling strategy Table 5 in section 3.4.2.<br>• Update number of complete cycle formula in section 3.3.8<br>• Section 3.4.4 remove AJCC prognostic stage subgroup<br>• Modify age subgroup to <65 years, >=65 years in sections 3.4.4 and 3.6<br>• Section 3.6.3 revised ALT/AST abnormal categories |

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# LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| **5-FU** | 5-fluorouracil |
| **AE** | Adverse event |
| **AESI** | Adverse events of special interest |
| **AJCC** | American Joint Committee on Cancer |
| **ALP** | Alkaline phosphatase |
| **ALT** | Aspartate amino transferase |
| **ANCOVA** | Analysis of Covariance |
| **aPTT** | Activated partial thromboplastin time |
| **AST** | Aspartate aminotransferase |
| **BMI** | Body mass index |
| **BOR** | Best overall response |
| **BSA** | Body surface area |
| **CA19-9** | Carbohydrate antigen 19.9 |
| **CI** | Confidence interval |
| **CR** | Complete response |
| **CRF** | Case report form |
| **CSR** | Clinical Study Report |
| **CT** | Computed tomography |
| **DOR** | Duration of response |
| **ECOG** | Eastern Cooperative Oncology Group |
| **eCRF** | Electronic case report form |
| **EORTC** | European Organisation for Research and Treatment of Cancer |
| **EQ VAS** | EuroQol Visual Analogue scale |
| **EQ-5D-5L** | EuroQol 5 dimension health status questionnaire (5 level) |
| **GHS** | Global health status |
| **HCG** | Human chorionic gonadotrophin |
| **HR** | Hazard Ratio |
| **HRQoL** | Health-related quality of life |
| **HSD** | Hwang-Shi-Decani |
| **IA** | Interim analysis |
| **ICE** | Intercurrent event |
| **IDMC** | Independent data monitoring committee |
| **INR** | International normalised ratio |
| **ITT** | Intention to treat |
| **IWRS** | Interactive Web Response System |
| **KM** | Kaplan-Meier |
| **LLN** | Lower limits of normal |
| **LOCF** | Last observation carried forward |
| **LV** | Leucovorin |
| **MedDRA** | Medical Dictionary for Regulatory Activities |
| **MRI** | Magnetic resonance imaging |
| **NCI-CTC** | National Cancer Institute – Common Toxicity Criteria |
| **NE** | Not evaluable |
| **ORR** | Overall response rate |
| **OS** | Overall survival |
| **PD** | Progressive disease |

| Abbreviation | Definition |
|---|---|
| **PFS** | Progression-free survival |
| **PK** | Pharmacokinetics |
| **PP** | Per protocol |
| **PT** | Preferred term |
| **PR** | Partial response |
| **PRO** | Patient Reported Outcome |
| **QLQ-C30** | Quality-of-life core 30 questionnaire |
| **QLQ-PAN26** | Quality-of-life questionnaire pancreatic cancer module |
| **QoL** | Quality of life |
| **QTcF** | QT interval corrected by Fridericia's formula |
| **RECIST** | Response Evaluation Criteria in Solid Tumours |
| **RS** | Raw score |
| **SAE** | Serious adverse event |
| **SAP** | Statistical Analysis Plan |
| **SD** | Stable disease |
| **SmPC** | Summary of Product Characteristics |
| **SOC** | System organ class |
| **TEAE** | Treatment-emergent adverse event |
| **TNM** | Tumor node metastasis |
| **TTF** | Time to treatment failure |
| **TTR** | Time to Response |
| **ULN** | Upper limits of normal |
| **USPI** | United States package insert |
| **WHODD** | World Health Organization Drug Dictionary |

# 1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a description of the statistical methods to be implemented for the analysis of data from the study with protocol number D-US-60010-001. The first version of the SAP was finalized prior to the first subject randomised. Any deviations from the SAP after database lock will be documented in the final Clinical Study Report (CSR).

# 2 STUDY OVERVIEW

## 2.1 Study Objectives

### *2.1.1 Primary Objective*

The primary objective of this study is to evaluate the efficacy of the regimen of irinotecan liposome injection + oxaliplatin + 5-fluorouracil (5-FU)/leucovorin (LV) versus nab-paclitaxel + gemcitabine in improving overall survival (OS) in subjects who have not previously received chemotherapy for metastatic adenocarcinoma of the pancreas.

### *2.1.2 Secondary Objectives*

The secondary objectives of this study are as follows:

- To evaluate progression free survival (PFS) according to Response Evaluation Criteria in Solid Tumours (RECIST) Version 1.1 guidelines
- To evaluate the overall response rate (ORR) according to RECIST Version 1.1 guidelines
- To evaluate the safety of this regimen in this patient population.

### *2.1.3 Exploratory Objectives*

- To evaluate time to deterioration of subjects in global health status (GHS), function domains, and disease related symptoms using patient reported outcome (PRO) data collected in the European Organisation for Research and Treatment of Cancer quality-of-life-core questionnaire (EORTC QLQ-C30).
- To evaluate the pharmacokinetics (PK), and the relationship between PK exposure and efficacy and safety, of the regimen of irinotecan liposome injection+oxaliplatin+5-FU/LV (Arm 1)
- To compare time to treatment failure (TTF) between treatment arms
- To compare duration of response (DOR) between treatment arms
- To compare time to response (TTR) between treatment arms
- To describe the possible association between genotypes to include but not be limited to UGT1A1*28 allele status, SN-38 concentration (only for subjects treated with irinotecan liposome injection+oxaliplatin+5-FU/LV) and safety
- To explore the pharmacodynamic biomarker CA 19-9 for the regimen of irinotecan liposome injection+oxaliplatin+5-FU/LV compared with nab-paclitaxel+gemcitabine in this patient population.
- To conduct biobanking of samples for future analysis of biomarkers amongst subjects who consent to optional biobanking.

- To collect gene mutation and genomic alteration status associated with pancreatic adenocarcinoma of subjects determined prior to screening (if available).

## 2.2 Study Design

### *2.2.1 General Design and Study Schema*

This is an open-label, randomised, multicentre, phase III study to evaluate the efficacy and safety of the irinotecan liposome injection+oxaliplatin+5-FU/LV combination regimen versus nab-paclitaxel+gemcitabine in adult subjects with metastatic adenocarcinoma of the pancreas.

After informed consent is obtained and subjects have been successfully screened, subjects will be randomised in a 1:1 ratio to one of the following treatment regimens:

- Arm 1: irinotecan liposome injection+oxaliplatin+5-FU/LV
- Arm 2: nab-paclitaxel+gemcitabine.

Approximately 750 subjects are planned to be randomised (1:1 approximately 375 subjects per arm).

The study will be completed once all subjects have discontinued the study treatment and at least 543 OS events have occurred in the randomised subjects.

### *2.2.2 Randomization and Blinding*

This is an open-label study.

The sponsor's randomisation manager or a designee, who is a statistician independent from the study, will prepare a list of randomisation numbers. It will be produced in blocks, on a balanced ratio [1:1] and will be stratified according to:

- Eastern Cooperative Oncology Group (ECOG) performance status (0/1)
- Region (North America/East Asia/Rest of the World)
- Liver metastases (Yes/No).

### *2.2.3 Study Treatments*

Irinotecan liposome injection will be administered in combination with oxaliplatin and 5-FU/LV, as follows:

Arm 1: Doses and administration of irinotecan liposome injection, oxaliplatin, 5-FU/LV, on Days 1 and 15 of each 28-day cycle.

The comparator treatment will be administered as follows:

Arm 2: Doses and administration of nab-paclitaxel and gemcitabine (established doses as per United States package insert (USPI) and EU Summary of Product Characteristics (SmPC) nab-paclitaxel), on Days 1, 8 and 15 of each 28-day cycle:

### *2.2.4 Sample Size Determination*

The primary objective of this study is to compare OS in subjects treated with irinotecan liposome injection+oxaliplatin+5-FU/LV to OS in subjects treated with nab-paclitaxel+gemcitabine.

Approximately 750 subjects will be randomised in a 1:1 ratio to the two treatment arms. Accounting for the planned interim analysis, follow-up until at least 543 OS events are observed across the two treatment

arms provides at least 90% power to detect a true hazard ratio (HR) of HR≤0.75 (modified OS: 9 versus 12 months) using a stratified log-rank test with overall 1-sided significance level of 0.025 (adjusted for interim analysis). The study plans to enrol 750 subjects. For operational purposes, the expected timing of the final analysis triggering event will be periodically projected using blinded study data regardless of treatment arm. The sample size may be increased if a review of the accumulating OS events suggests that the timing of the final analysis will be extended.

Assuming enrolment over 16 months increasing to approximately 62 subjects per month and lost-to-follow-up rate of 5% across both treatment arms, the timing of the interim analysis, estimated via simulation, is expected to be at 24 months after the first subject treated and the timing of the final analysis is expected to be at 36.5 months after the first subject treated.

If blinded projection of the accumulating OS events suggests that the number required for the final analysis will not be reached (due to censoring) within 32 months of study initiation, the sample size may be increased up to 800 subjects or until prespecified events are met, whichever comes earlier. The projection to inform the decision to potentially increase the number of subjects will be carried out within 3 months prior to expected completion of planned enrolment of 750 subjects.

There are two planned analyses for OS: interim analysis (IA) and final analysis. The IA is planned when at least 272 OS events (i.e. 50% information time) have been observed in the Intention to treat (ITT) population. If that analysis does not indicate futility or efficacy, then the final analysis is planned at least 543 OS events when 100% of the planned number of subjects have been enrolled. The overall type I error is controlled at 1-sided significance level of 0.025 (adjusted for interim analysis).

An alpha and beta spending function according to Hwang-Shi-Decani (HSD) $\gamma_{alpha}$=-4 and $\gamma_{beta}$=-1 will be utilised to control type I and type II errors for the OS comparison. In the computation of the type I error rate, futility analyses are considered non-binding. Since the futility and efficacy boundary is dependent on the number of OS events, the actual boundary used will be re-calculated, incorporating the spending function, as defined, based on the number of actual OS events analysed at the time of analysis. P-boundary will be used as the criteria for the formal statistical inference.

The interim analysis specifications per the plan are provided in Table 1.

**Table 1 Type I (α) and Type II (β) Error Spending for the Planned Analyses (α = 0.025)**

| | | Futility | | | | Efficacy | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Analysis** | **D** | **$Z_{boundary}$** | **$p_{boundary}$** | CUM β spend | $HR_{crit}$ | **$Z_{boundary}$** | **$p_{boundary}$** | CUM α spend | $HR_{crit}$ |
| **Interim** | 272 | -0.592 | 0.277 | 0.038 | 0.931 | -2.750 | 0.003 | 0.003 | 0.716 |
| **Final** | 543 | -1.981 | 0.024 | 0.100 | 0.844 | -1.981 | 0.024 | 0.025 | 0.844 |

D = # of OS events at analysis. Z-boundary is the critical test statistic value at which futility (< Z) or efficacy (> Z) would be concluded. P-boundary is the critical one-sided p-value threshold for the comparison. Cum α-spend and cum β-spend are the amount of cumulative type I and type II error spent at each analysis, respectively. HRcrit is the observed hazard ratio threshold (> HR for futility, < HR for efficacy).

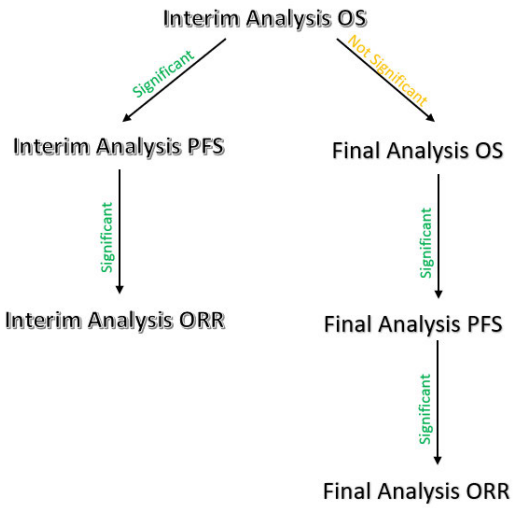
The Independent data monitoring committee (IDMC) will be responsible for evaluating the interim analyses and making a recommendation about early termination due to observed study results from the interim analyses. Details are documented in the separate IDMC charter.

### *2.2.5 Significance Testing and Estimations*

Secondary efficacy endpoints (PFS and ORR) will only be evaluated if the primary efficacy endpoint demonstrates superiority for irinotecan liposome injection+oxaliplatin+5 FU/LV over nab paclitaxel+gemcitabine. If the primary endpoint of OS is declared significant at the interim, secondary endpoints will be tested at the interim. Otherwise, secondary efficacy endpoints will be tested at the final analysis if OS is found to be statistically significant at that analysis. Hypothesis testing of secondary endpoints will be conducted in a stagewise hierarchical manner incorporating alpha spending for each endpoint using HSD γalpha= -4, similar to that specified for the primary efficacy analysis. The nominal level for each comparison will depend on whether the analysis is carried out at the interim or at the planned final analysis.

The first endpoint in the hierarchy of secondary endpoints will be PFS. If OS and PFS are both significant, then ORR would be tested. Any parameter which is not formally tested for significance (per the hierarchy) will be regarded as descriptive and exploratory.

Figure 1 Primary and Secondary Endpoints Analyses Flow Chart




The first endpoint in the hierarchy of secondary endpoints will be PFS. If OS and PFS are both significant, then ORR would be tested. Figure 1 illustrates the testing strategy of primary and key secondary endpoints.

- If OS is significant at the interim analysis, the analysis of secondary endpoints will be performed at the interim analysis.
- If OS is not significant at the time of the interim analysis but is significant at the final analysis, the analysis of secondary endpoints will be performed at the final analysis only.
- If OS is not significant after either the interim analysis or the final analysis, secondary endpoints will not be statistically evaluated.

Any parameter which is not formally tested for significance (per the hierarchy) will be regarded as descriptive and exploratory.

Hypothesis testing of key secondary endpoints will be conducted in a stagewise hierarchical manner [Glimm 2010] incorporating alpha spending for each endpoint using HSD $\gamma_{alpha}$= -4, same as that specified for the final analysis. The nominal level for each comparison will depend on whether the analysis is carried out at the OS interim or at the planned OS final analysis.

HSD $\gamma_{alpha}$ error spending function $=\alpha(1-e^{-\gamma t})/(1-e^{-\gamma})$ with 1 sided α=0.025 and γ=-4.

The information fraction at each analysis will be calculated based on the actual number of events observed at the time of analysis if the actual number of events observed is different from planned for OS. The information fraction of OS and PFS will be based on the actual number of events observed at the time of analysis and the information fraction of ORR will be based on the number of subjects randomized in the study.

## 2.3 Study Endpoints

### *2.3.1 Primary Endpoint*

The primary efficacy endpoint is the OS of subjects randomised to irinotecan liposome injection+oxaliplatin+5-FU/LV compared to subjects randomised to nab-paclitaxel+gemcitabine.

Survival will be defined, in the standard way for OS evaluation, as time from the date of randomisation to the date of death (any cause).

### *2.3.2 Secondary Endpoints*

PFS and ORR endpoints will only be evaluated if the primary efficacy endpoint demonstrates superiority for irinotecan liposome injection+oxaliplatin+5-FU/LV over nab-paclitaxel+gemcitabine. Investigator-assessed tumour response will be used in efficacy analysis. Tumour response will be evaluated according to the RECIST Version 1.1 [Eisenhauer 2009].

Progression Free Survival

The PFS is the time from randomisation to the first documented objective disease progression using RECIST Version 1.1 or death due to any cause, whichever occurs first.

PFS will be calculated as follows:

PFS (months) = (Event or Censoring Date – Date of Randomisation + 1)/30.4375

Determination of PFS will be per investigator assessment. Subjects will have computed tomography (CT) scans (or MRI if the subject is allergic to CT contrast media) performed every 8 weeks that will be evaluated by the investigator site using RECIST guidelines Version 1.1. After end of treatment visit, for subjects who discontinue the study for reasons other than radiologically confirmed disease progression only and have not started any further subsequent anti-cancer treatment will have scan every 2 months, or 8 weeks.

Overall Response Rate

The ORR is defined as the proportion of subjects with a best overall response (BOR) characterised as either a complete response or partial response per RECIST Version 1.1.

Safety Endpoints

Safety will be monitored through continuous reporting of AEs and serious adverse events (SAEs), laboratory abnormalities, incidence of subjects experiencing dose modifications (including infusion

interruptions, dose omissions and dose delays) and/or premature discontinuation of study treatment (and reason for discontinuation).

- Adverse Events

  Adverse events (AEs) will be monitored from the time that the subject gives informed consent until 30 days after the last dose of study medication. All AEs will be coded according to Medical Dictionary for Regulatory Activities (MedDRA) Version 22.0 or later and will be classified by MedDRA preferred term and system organ class.

  A treatment emergent adverse event (TEAE) is defined as any AE that occurs during the active phase of the study (between first dose of study treatment and 30 days after the end of study treatment) if:

  - it was not present prior to receiving the first dose of study medication, or
  - it was present prior to receiving the first dose of study medication but the grade increased or became serious during the active phase of the study, or
  - it was present prior to receiving the first dose of study medication, the grade/seriousness is the same but the causality changed to "related" during the active phase of the study.

  Adverse events of special interest (AESIs) are thrombo-embolic events, National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v5.0) Grade 1 to 5. These AESI will be collected in the case report form (CRF) using the AESI reporting option on the AE page of the eCRF.

- Clinical Safety Laboratory Tests

  Haematology blood samples will be collected to assess the following variables: haemoglobin, WBC count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils and others), platelet count and coagulation (Prothrombin Time with International Normalised Ratio (INR) and Activated Partial Thromboplastin Time (aPTT)).

  Serum biochemistry will be analysed centrally but can also be analysed locally (optional) in the case of requiring timely results. If local laboratory results are required, the local laboratory ranges for upper limit of normal (ULN) and lower limits of normal (LLN) should be included in the reporting. Central laboratory samples should always be taken, even if local laboratory samples have also been taken: creatinine, total bilirubin, conjugated bilirubin, sodium, potassium, calcium, phosphate, alkaline phosphatase (ALP), aspartate amino transferase (AST), aspartate aminotransferase (ALT), gamma glutamyl transferase, albumin, and total protein.

  Urinalysis (dipstick) will be undertaken.

- Pregnancy Test

  A urine or beta human chorionic gonadotrophin (HCG) serum test will be performed locally for all female subjects of childbearing potential.

- 12-lead 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, clinical significance or non-significance should be indicated.

Standard 12-lead ECG parameters include sinus rhythm (yes/no), RR interval, PR interval, QRS duration, QT interval, QT interval corrected by Fridericia's formula (QTcF) interval, and interpretation of clinical significance.

- Vital signs

  Vital signs include height (at screening only) weight, resting blood pressure, pulse and temperature.

- Physical Examination

  Physical examinations will be conducted as per schedule of assessments. Any clinically significant physical examination findings (abnormalities) observed during the study will be reported.

- ECOG performance status

  The ECOG performance status will be recorded at the timepoints per schedule of assessments. The ECOG will be assessed by the investigator or his/her designee via questioning of the subject about their functional capabilities.

### *2.3.3 Exploratory Endpoints*

Patient-Reported Outcomes

The PRO exploratory endpoints are as follows:

- Assess time to deterioration or worsening of subjects GHS, physical functioning, disease related symptoms of interest using EORTC-QLQ-C30 in Appendix D
- Summarise Health-related quality of life (HRQoL) score at each visit as assessed by QLQ-C30, QLQ-PAN26, PRO-CTCAE and EQ-5D-5L.

Pharmacokinetics

The pharmacokinetics (PK), and the relationship between PK exposure and efficacy and safety, of the regimen of irinotecan liposome injection+oxaliplatin+5-FU/LV (Arm 1) in this patient population will be evaluated.

Time to Treatment Failure

The TTF is defined as the time from randomisation to treatment discontinuation for any reason, including

- progressive disease per RECIST,
- progressive disease clinical,
- adverse event,
- death,
- withdrawal by subject,
- protocol deviation,
- physician decision,
- site terminated by sponsor,
- study terminated by sponsor,
- lost to follow-up,
- pregnancy,
- any other reasons collected in the eCRF, or

- initiation of subsequent anti-cancer therapy (drug therapy, curative radiotherapy, curative surgery) including new antineoplastic treatment.

Duration of Response (DoR)

DOR is defined as the time of initial response (complete response or partial response) until documented objective tumor progression using RECIST Version 1.1 or death. DoR will be computed only for subjects who achieved complete response or partial response. For subjects who do not have documented disease progression or death, DOR will be censored following the same rules as PFS specified in Table 3.

Time to Response

TTR is defined as the time from randomisation to the first documented objective tumor response (CR or PR) using RECIST Version 1.1. TTR will be computed only for subjects who achieved complete response or partial response.

Genotyping: UGT1A1 and SN-38

The possible association between genotypes to include but not limited to UGT1A1*28 and other UGT1A genotypes, SN-38 concentration (only for subjects treated with irinotecan liposome injection+oxaliplatin+5-FU/LV) and safety will be described.

Biomarkers CA 19-9

The biomarker CA 19-9 concentrations will be measured and compared between treatment arms.

Biobanking

The exploratory endpoint comprises biobanking of samples for future analysis, among subjects who consent. Analysis of biobank samples will be performed outside the scope of the main study and reported separately.

Gene Mutations and Genomic Alterations

The exploratory endpoint comprises of collection of gene mutation and genomic alteration status associated with pancreatic adenocarcinoma of the subjects, determined prior to screening where available. Several genes are associated with an increased risk of developing PDAC. Those of key interest include:

- Germline mutations and genomic alterations: BRCA1, BRCA2, PALB2, ATM , CDKN2A, MLH1, MSH2, MSH6, TP53 and EPCAM.
- Somatic mutations and genomic alterations: KRAS, TP53, CDKN2A, SMAD4, RNF43, ARID1A, TGFβR2, GNAS, RREB1 and PBRM1.

Analysis will be performed outside the scope of the main study and results reported separately.

# 3 STATISTICAL METHODOLOGY

## 3.1 General Considerations

### *3.1.1 Analysis Day*

Analysis day will be calculated from the date of randomization. The day of the randomization will be Day 1, and the day immediately before Day 1 will be Day -1. There will be no Day 0.

### *3.1.2 Analysis Visits*

No study visit windows will be used for analyses.

### *3.1.3 Definition of Baseline*

Baseline for a safety assessment is defined as the last non-missing measurement on or prior to the first dose of study treatment.

Baseline for an efficacy assessment is defined as the last non-missing measurement, including unscheduled assessment on or prior to the date of the randomisation. If a subject's first assessment occurs after randomisation but prior to the first dose, this assessment will be used as the baseline.

For ECOG, baseline is defined as the last observed measurement on or prior to the date of the randomization.

For all PRO assessments, baseline is defined as the last observed measurement on or prior to first drug administration at C1D1.

### *3.1.4 Summary Statistics*

Categorical variables will be summarised by frequency distributions (number and percentage of subjects). Percentages given in these tables will be rounded and, therefore, may not always sum to 100.0%. Continuous variables may be summarised by a clinically relevant discretization of the variable.

All confidence intervals (CIs) for parameters to be estimated will be constructed with a significance level $\alpha = 0.05$ (i.e. a 95% CI).

Time to event distribution (e.g. progression free survival, overall survival, time to response, and duration of response) will be estimated using Kaplan Meier methodology. Median survival time along with 95% CI will be constructed based on a log-log transformed CI for the survival function S(t). Rates at fixed time points will be derived from the Kaplan Meier estimate and corresponding confidence interval will be derived based on Greenwood formula for variance derivation and on log-log transformation applied on the survival function S(t).

Minimum and maximum will be reported to the same precision as the collected data, mean and median will be reported to one additional decimal place, and standard deviation will be reported to two additional decimal places. Some discretion may be applied. Confidence intervals will be reported to the same precision as the summary statistic for the interval (e.g., the confidence interval for a mean will be reported to the same precision as the mean). P-values will be reported to 4 decimal places.

The stratification factors are captured in the interactive web response system (IWRS) and on electronic case report forms (eCRFs). The primary efficacy analysis (OS) and key secondary efficacy analyses (PFS and ORR) will use the randomization stratification factors from IWRS. Unless otherwise specified, all stratified analyses will be based on the stratification factors per eCRF. A cross tabulation of the frequency of each level of each stratification factor per IWRS and eCRF will be produced.

### *3.1.5 Study Hypothesis*

Irinotecan liposome injection+oxaliplatin+5-FU/LV has superior efficacy over nab-aclitaxel+gemcitabine, demonstrated by a 3-month improvement in OS, in the treatment of subjects who have not previously received chemotherapy for metastatic adenocarcinoma of the pancreas.

### *3.1.6 Evaluation of Site Effect*

It is not planned to perform a subgroup analysis on individual centres. Region is a randomsition stratification factor and is one of the planned variables to perform subgroup analyses.

### *3.1.7 Handling of Missing Data*

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:

1) 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 active phase (i.e. a TEAE for AEs) except if the partial onset date or other data [stop date, …] indicates differently).

2) A missing/incomplete date of medical history or disease diagnosis will be assumed to have occurred before any study treatment.

3) If a partial date and the associated information do not allow to state about the assignation to a group / category, all the possible groups / 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).

4) Where this is possible, the derivations based on a partial date will be presented as superior inequalities (i.e.: for an AE started in FEB2021 after the administration performed on 31JAN2021, the days since last dose will be "≥2", similarly the duration of ongoing AEs or medication will be"≥xx" according to the start and last visit dates).

Other rules for handling missing data related to endpoints are described in the endpoint definitions (Section 2.3) or in the description of analyses (Section 3).

### *3.1.8 Handling of Repeated and Unscheduled Measurements*

All repeated and unscheduled measurements will be presented in the listings, where applicable.

Both scheduled and unscheduled results will be considered in clinical laboratory, ECG and vital sign tables.

## 3.2 Analysis Populations

### *3.2.1 Screened Population*

All subjects screened (i.e. who signed the informed consent).

### *3.2.2 Intent-to-Treat Population*

This population includes all randomised subjects to whom study treatment has been assigned by randomization. A subject is randomised (after informed consent has been provided) if there is confirmation of successful allocation of a randomization number through IWRS. According to ITT principle, subjects will be analyzed according to the treatment and strata they have been assigned to during the randomization procedure.

### *3.2.3 Per-Protocol (PP) Population*

This is a subset of the ITT population. It includes subjects who have no major protocol deviations that could potentially affect the primary efficacy analysis for the subject as described in the protocol deviations document.

### *3.2.4 Safety Population*

The safety population is a subset of the ITT population that received at least one dose (including a partial dose) of any component of the study medication in the combination therapy). Subjects will be analyzed according to study treatment actually received.

### *3.2.5 PRO Population*

All subjects of the randomised ITT population that have provided baseline and at least one subsequent assessment on each PRO instrument.

### *3.2.6 Pharmacokinetics Population*

All subjects who received at least one dose and who have at least one plasma concentration and no major protocol deviations affecting PK variables.

PK sampling is performed in Arm 1 (irinotecan liposome injection+oxaliplatin+5-FU/LV) only.

## 3.3 Subject Data and Study Conduct

### *3.3.1 Subject Disposition*

The following subject disposition categories will be summarized by treatment arm and in total using screened population:

- Study treatment
    - Subjects who were screened
    - Subjects who were randomised
    - Subjects who were not randomised and reasons
    - Subjects who were randomised but not treated
    - Subjects who received study treatments
    - Subjects who received non-planned study treatments
    - Subjects with ongoing study treatments
    - Subjects who permanently discontinued from study treatment
        - Subjects who permanently discontinued from study treatment due to COVID-19 pandemic
        - Primary reasons for treatment discontinuation
- Long-term follow up
    - Subjects who entered long-term follow up
    - Subjects with ongoing long-term follow up
    - Subjects who discontinued from long-term follow up
- Study
    - Subjects who discontinued from study
        - Subjects who discontinued from study due to COVID-19 pandemic

- Primary reasons for end of study

- Survival status at data cut-off
  - Alive
  - Death
  - Lost to Follow up

Subjects who were randomised by country and site, and by treatment arm and overall will also be summarized using ITT population.

Subject disposition, inclusion and exclusion criteria, assessment visits, randomization and withdrawal of consent will be listed.

### *3.3.2 Protocol Deviations*

Any major and minor protocol deviation will be documented as described in the protocol deviation plan, and its impact on inclusion in each analysis population for any subject will be specified. The final list of protocol deviations impacting the analysis populations will be reviewed prior to database lock.

Counts and percentages of subjects with major protocol deviations by deviation category and by COVID-19 relationship will be summarised using ITT population. Study visits impacted by COVID-19 will be summarized and listed.

Major protocol deviations and subjects excluded from analysis population will be listed using ITT population.

### *3.3.3 Analysis Populations*

The numbers and percentages of subjects enroled and included in each analysis population will be tabulated using ITT population. The reasons for subject exclusions from each of the analysis populations will also be tabulated.

Analysis population will be listed with subject disposition.

### *3.3.4 Demographic and Baseline Characteristics*

Descriptive summary statistics (n, mean, standard deviation, median, minimum, maximum) or frequency counts of demographic and baseline data will be presented by treatment group on the ITT population. No formal statistical analysis will be performed on these data.

Demographic characteristics will include

- age (years),
- age category (<65 years, ≥65 years [65-75years, >75+ years]),
- sex (male, female),
- ethnicity (Hispanic or Latino, Not Hispanic or Latino, not reported),
- race (Asian, American Indian or Alaska Native, Black or African American, Native Hawaiian or Other Pacific Islander, White, not reported, Other),
- baseline weight (kg),
- baseline height (cm),
- baseline body mass index (BMI) in $kg/m^2$,
- baseline body surface area (BSA) ($m^2$)
- baseline albumin (g/L),

- baseline CA 19-9 (U/mL),
- baseline CA 19-9 category (<37 U/mL, ≥37 U/mL),
- baseline UGT1A1*28 allele status (homozygous/non-homozygous),
- baseline ECOG performance status (0, 1),
- liver metastases (yes, no) and
- geographic location (North America/East Asia/Rest of the World).

Note: Some countries may not collect race and/or ethnicity information. Baseline ECOG, liver metastases and geographic location are based on eCRF data.

Baseline disease characteristics will include

- time from initial diagnosis of pancreatic adenocarcinoma until date of randomization (weeks),
- time from diagnosis of metastatic disease at study entry until date of randomization (weeks),
- stage of original diagnosis,
- histological grade,
- American Joint Committee on Cancer (AJCC, 8th edition) prognostic stage (I-III, IV) at study entry,
- number of metastatic sites (0, 1, 2, ≥3),
- selected metastatic site (liver, lung) and
- main pancreatic tumor location (head, body, tail, unknown).

Prior cancer therapy will include

- prior anti-cancer therapy for pancreatic cancer (yes, no),
- prior chemotherapy for pancreatic cancer (yes, no),
- prior radiotherapy for pancreatic cancer (yes, no),
- prior surgical procedures for pancreatic cancer (yes, no), and
- time from last anti-cancer treatment for pancreatic cancer until date of randomization (weeks),

AJCC prognostic stage group from AJCC 8th edition is derived from TNM staging collected from eCRF data (Appendix G).

Demographic, pancreatic adenocarcinoma history, disease history, and prior cancer therapy data will also be listed.

### *3.3.5 Baseline stratification factors*

The number (%) of subjects in each stratum based on data obtain from IWRS will be summarized overall and by treatment arm for the ITT. Discordances between the stratum records in the IWRS at the time of randomization and the actual stratum recorded in the clinical databased through the data collected on the eCRF will be cross-tabulated and listed.

### *3.3.6 Medical History*

Medical and surgical history and baseline signs and symptoms related to cancer will be coded initially using the latest version of MedDRA in use in Ipsen system.

Listings will present the preferred term and verbatim text.

Frequency tables of the number and percentage of subjects will be provided for medical and surgical history and baseline signs and symptoms related to cancer by system organ class (SOC) and preferred term (PT) using ITT population.

### *3.3.7 Prior and concomitant Medications*

Prior, concomitant, and post-treatment medications are defined as following:

- Prior medications will include medications which started prior to the first study treatment administration date, but exclude medications captured on Prior Chemotherapy, Hormonal and Immunotherapy for Pancreatic Cancer or Other Cancer CRF.
- Concomitant medications will include medications taken any time from the first study treatment administration date through 30 days following the last study treatment administration date or until the start of a subsequent anti-cancer therapy(drug therapy, curative radiotherapy, curative surgery), whichever is earlier. Medications that started prior to the first dose of study treatment but continued into treatment are considered concomitant.

Prior, concomitant medications, and further subsequent anti-cancer therapy will be coded using the latest version of World Health Organization Drug Dictionary (WHODD) in use in Ipsen system.

Frequency tables of the number and percentage of subjects will be provided using ITT population for prior medications, concomitant medications, and prior chemotherapy, hormonal and immunotherapy for pancreatic cancer separately by therapeutic class and PT for each treatment arm. Listings will be presented for the therapeutic class, PT and verbatim text.

Further subsequent anti-cancer therapy (drug therapy, curative radiotherapy, curative surgery) collected in eCRF will be summarized separately. Pre-medications and all further subsequent anti-cancer treatments including regimen name, start and stop dates, best response, and reason of discontinuation will be listed.

Concomitant surgical procedures, and prior and concomitant non-drug therapies will be coded initially using the latest version of MedDRA in use in Ipsen system. Frequency tables of the number and percentage of subjects will be provided by PT on safety population for concomitant surgical procedures, and prior and concomitant non-drug therapies by system organ class and preferred term. Listing will be provided.

Additionally, a listing of prior and concomitant blood transfusions will also be provided.

### *3.3.8 Study Treatment Exposure*

The following summaries will be presented using safety population by each study treatment (irinotecan liposome injection, oxaliplatin infusion, leucovorin infusion, 5-FU infusion, nab-paclitaxel injection, and gemcitabine injection) and treatment arm:

- Last date of exposure to study drug = last dose date of study treatment + planned days to next dose. Arm 1 irinotecan liposome injection, oxaliplatin, 5-FU/LV planned days to next dose is 14 days. Arm 2 nab-paclitaxel+gemcitabine planned days to next dose is 7 days if the last dose occurs on Day 1 or Day 8 of a cycle and is 14 days if last dose occurs on Day 15 of a cycle.

  If a patient died or was withdrawal of study consent and/or lost to follow-up before the derived last date of exposure, the last date of exposure of study drug is the date of death or the date of last contact before withdrawal of study consent and/or lost to follow up respectively. If the derived last date of exposure goes beyond the date of cutoff date, it should be truncated to the date of data cutoff.

- Duration of exposure to study drug (week) = (last exposure to study drug - first dosing date of study drug +1) / 7 (period of dose interruption are not excluded)

Duration of exposure to a treatment arm (week) = [The last day of exposure to any study drug of a non-zero dose administrated – earliest dosing date of any study drug with a non-zero administrated +1]/ 7 (period of dose interruption are not excluded)

- Total number of treatment cycles administered
- Total number of treatment cycles of study treatment administered categorized as follows:
    - Cycle 1
    - Cycle 2
    - Cycle 3
    - Cycle 4
    - Cycle 5
    - Cycle 6
    - Cycle 7
    - Cycle 8 or more
- The number and percentage of subjects with infusion interruptions/dose adjustments including:
    - Dose reductions
    - Dose delays
    - Drug withdrawals
    - Dose omitted

The following summaries will be provided by each study treatment only.

- Cumulative actual dose administered (mg/m$^2$), calculated as

$$\sum_k \frac{actual\ dose\ (mg)\ at\ Dx\ for\ cycle\ k}{BSA\ (m^2) at\ Dx\ for\ cycle\ k}$$

  where Dx is the dosing day in each arm. BSA will be calculated using weight and height within a dosing day based on Dubois equation. If a subject has missing BSA due to missing weight and/or height on a dosing day, the last observation carried forward (LOCF) approach will be used.

- Cumulative planned dose will be calculated in the same manner as cumulative actual dose but using planned dose per cycle times number of complete cycles. If a subject has dose skip or discontinues the treatment, the planned dose (mg) and BSA (m$^2$) in the missing dosing visits will be imputed using LOCF method.
    - number of complete cycle = (last dosing date of study drug – first dosing date of study drug + 1) / 28
- Overall actual dose intensity (ADI) administered (mg/m$^2$/week), calculated as

$$ADI = \frac{Cumulative\ actual\ dose\ administered\ (mg/m^2)}{Duration\ of\ exposure\ (week)}$$

- Overall planned dose intensity (PDI) (mg/m$^2$/week), calculated as

$$PDI = \frac{Cumulative\ planned\ dose\ administered\ (mg/m^2)}{Planned\ \ duration\ of\ exposure\ (week)}$$

  where planned treatment duration = 4 weeks * the number of complete cycles.

- Overall relative dose intensity (RDI) (%), calculated as

$$RDI\ (\%) = \frac{ADI}{PDI} \times 100$$

- Actual dose intensity administered by cycle
- Planned dose intensity administered by cycle
- Relative dose intensity administered by cycle

All information collected on the eCRF related to for each study treatment including planned dose, actual dose, any dose adjustments will be listed.

## 3.4 Efficacy Analysis

The ITT population is the primary population for all demographic, baseline disease characteristics, and efficacy parameters. All analyses using this population will be based on the treatment assigned by IWRS.

In addition, PP analysis may be performed as secondary/confirmatory. Subjects will be analysed as randomised.

### *3.4.1 Primary Efficacy Endpoint Analysis*

#### *3.4.1.1 Overall Survival*

OS will be calculated as follows:

OS (months) = (Death or Censoring Date – Date of Randomisation + 1)/30.4375

All death occurring on or before the cut-off date in the ITT will be used in the OS analysis. Subjects who do not have a date of death recorded at the time of the final analysis will be censored at the last known time that the subject was alive. For each subject who is not known to have died as of the data-inclusion cut-off date for a particular analysis, OS will be censored for that analysis at the date of the last known time that the subject was alive prior to the data cut-off date.

Primary Analysis

The OS for each treatment arm will be summarised by median survival time and its 95% CIs from Kaplan-Meier (KM) estimation. Stratified analyses, based on the randomisation stratification factors per IWRS, will be used for treatment comparisons on the ITT population. Differences in the OS curves will be tested using a stratified and unstratified log-rank test separately. The estimated treatment effect for Arm 1 will be summarised by the HR (including 95% CI) from stratified and unstratified Cox regression analysis separately. The Kaplan Meier curves of the two treatment arms with HR and 95% CI will be presented. KM based OS rates at 3, 6, 9, 12, and 18 months will be estimated and associated two-sided 95% CIs will be provided.

KM curve will be plotted by treatment arm on ITT and PP population respectively.

OS data will be listed by treatment arm and subject.

Sensitivity Analyses

The following additional sensitivity analyses may be carried out for OS on the ITT population and/or PP population to evaluate the robustness of the primary analysis results:

- log-rank comparisons of treatments on the PP population

- log-rank test comparisons of treatments with OS censored at the date where any post-treatment anti-cancer therapy (drug therapy, curative radiotherapy, curative surgery) is first administered on the ITT population

Primary efficacy endpoint in estimand framework is described in Table 2.

**Table 2 Primary Efficacy Endpoint in Estimand Framework**

| **Statistical category** | **Estimand:**<br>**Treatment:** Randomized Arm 1 (irinotecan liposome injection+oxaliplatin+5-FU/LV) or Arm 2 (nab-paclitaxel+gemcitabine).<br>**Population:** Subjects who have not previously received chemotherapy for metastatic adenocarcinoma of the pancreas as specified in the inclusion and exclusion criteria (Protocol Section 4.1 and Section 4.2), respectively.<br>**Endpoint (Variable)**: Overall survival, defined as the time from randomization date to the date of death.<br>**Intercurrent events:**<br>1. Start of subsequent anti-cancer therapy (drug therapy, curative radiotherapy, curative surgery) including new antineoplastic treatment<br>2. Permanently discontinuation from study treatment due to any reasons | | |
|---|---|---|---|
| | **Analysis set** | **Intercurrent event handling strategy** | **Population-level summary (Analysis):** |
| Primary | ITT | 1. Treatment policy strategy: ICE 1 and 2 will not affect the assessment of OS. | Treatment comparison using a stratified log-rank test and HR estimated by stratified Cox regression model. |
| Sensitivity 1 | PP | As primary | As primary |
| Sensitivity 2 | ITT | 1. Hypothetical strategy: Patients with ICE 1 will be censored at the date when any post-treatment anti-cancer therapy (drug therapy, curative radiotherapy, curative surgery) is first administered<br>2. Treatment policy strategy: ICE 2 will not affect the assessment of OS. | As primary |

### *3.4.2 Secondary Efficacy Endpoint Analysis*

The secondary efficacy endpoints will be analyzed at the time of the OS analysis (interim or final), only if the OS analysis crosses the stopping boundary.

#### *3.4.2.1 Progression Free Survival*

PFS will be calculated as follows:

PFS (months) = (Event or Censoring Date – Date of Randomisation + 1)/30.4375

Determination of PFS will be per investigator assessment using RECIST guidelines Version 1.1.

General censoring rules for the analysis of PFS are described in Table 3.

**Table 3 Date of Event or Censoring for PFS**

| Situation | Date of progression or censoring | Outcome | Description in TLFs |
|---|---|---|---|
| No evaluable baseline tumour assessment | Date of randomisation | Censored | Censored on Day 1 |
| No evaluable post-baseline tumour assessment | | | |
| Documented disease progression or death after missing ≥2 consecutive scheduled tumour assessments* of baseline or the last non-PD tumour assessment | Date of last evaluable tumour assessment prior to the first missed assessment<br>or<br>Date of randomisation | Censored | ≥2 consecutive missing tumour assessments |
| Documented disease progression within 2 consecutive scheduled tumour assessments* of baseline or the last non-PD tumour assessment | The Earliest of:<br>• date of tumour assessment showing new lesion (if progression based on new lesion) or<br>• date of tumour assessment of target/non-target lesions in which progression is documented | Event | Progression disease |
| Death within 2 consecutive scheduled tumour assessments of last the non-PD tumour assessment | Date of death | Event | Death |
| Withdrawal of study consent and/or lost to follow-up without documented disease progression or death | Date of the last evaluable tumour assessment prior to withdrawal of study consent and/or lost to follow-up<br>or<br>Date of randomisation if no post-baseline tumor assessment | Censored | Withdrawal of study consent and/or lost to follow up |
| Subsequent anti-cancer therapy (drug therapy, curative radiotherapy, curative surgery including subsequent antineoplastic treatment) started without disease progression or death | Date of the last evaluable tumour assessment prior to starting subsequent anti-cancer therapy (drug therapy, curative radiotherapy, curative surgery) including new antineoplastic treatment<br>or | Censored | Subsequent anti-cancer therapy |

| Situation | Date of progression or censoring | Outcome | Description in TLFs |
|---|---|---|---|
| | Date of randomisation if no post-baseline tumor assessment | | |
| None of the following:<br>• disease progression or death<br>• 2 consecutive missing scheduled tumour assessments<br>• Withdrawal of study consent and/or lost to follow-up<br>• Subsequent anti-cancer therapy | Date of the last evaluable tumour assessment<br>or<br>Date of randomisation if no post-baseline tumor assessment | Censored | Censored on last tumour assessments |

*Two consecutive post-baseline tumor assessments are based on protocol scheduled tumor assessments. The window of the tumor assessment is considered. Subjects are expected to have scans every 8 weeks, a subject who goes more than 18 weeks (16 weeks + 2 week) without a scan is considered missing 2 consecutive scheduled tumour assessments. If patients had subsequent anti-cancer therapy, missing 2 consecutive scheduled tumour assessments and withdrawal of study consent or lost to follow-up on same date, censored reason will be assigned in the order of 2 consecutive scheduled tumour assessments > anti-cancer therapy > withdrawal of study consent or lost to follow-up.

Main analysis of PFS will be performed on ITT populations using the same approach as primary analysis (see Section 3.4.1.1).

Sensitivity analysis will be repeated on PP population. A sensitivity analysis will be performed by applying treatment policy on withdrawal of study consent and/or lost to follow-up without documented disease progression or death on ITT population.

KM curves will be plotted by treatment arm on ITT and PP populations respectively.

The following information will also be summarized:

- Number and type of events (progression: RECIST 1.1, death),
- Number of subjects censored by type of censoring based on Table 3

PFS data will also be listed by treatment arm and subject.

The estimand of PFS is described in Table 4.

**Table 4 Secondary Efficacy Endpoint (PFS) in Estimand Framework**

| **Statistical category** | **Estimand:**<br>**Treatment:** Randomized Arm 1 (irinotecan liposome injection+oxaliplatin+5-FU/LV) or Arm 2 (nab-paclitaxel+gemcitabine).<br>**Population:** Subjects who have not previously received chemotherapy for metastatic adenocarcinoma of the pancreas as specified in the inclusion and exclusion criteria (Protocol Section 4.1 and Section 4.2), respectively.<br>**Endpoint (Variable)**: PFS, defined as the time from randomization date to the date of death or disease progression per RECIST v1.1.<br>**Intercurrent events:**<br>1. Start of subsequent anti-cancer treatment(drug therapy, curative radiotherapy, curative surgery) including new antineoplastic treatment<br>2. Withdrawal of study consent and/or lost to follow-up without documented disease progression or death<br>3. Two and more consecutively missing scheduled tumor assessments | | |
|---|---|---|---|
| | **Analysis set** | **Intercurrent event handling strategy** | **Population-level summary (Analysis):** |
| Secondary | ITT | Hypothetical strategy: Patients with ICE 1, 2 and 3 will be censored at last evaluable tumour assessment prior to starting subsequent anti-cancer therapy (drug therapy, curative radiotherapy, curative surgery) including new antineoplastic treatment, withdrawal of study consent and/or lost to follow-up or the first missed tumour assessment, respectively | Treatment comparison using a stratified log-rank test and HR estimated by stratified Cox regression model. |
| Sensitivity 1 | PP | As secondary | As secondary |
| Sensitivity 2 | ITT | 1. Hypothetical strategy: Patients with ICE 1 and 3 will be censored at last evaluable tumour assessment prior to starting subsequent anti-cancer therapy (drug therapy, curative radiotherapy, curative surgery) including antineoplastic treatment or the first missed tumour assessment, respectively<br>2. Treatment policy:<br>ICE 2 will not affect the analysis of PFS (i.e. tumor assessment or death after ICE 2 will be used in the analysis) | As secondary |

#### *3.4.2.2 Overall Response Rate*

The ORR is defined as the proportion of subjects with a best overall response (BOR) characterised as either a complete response or partial response per RECIST Version 1.1. ORR will be calculated based on the intent to treatment population as assessed by investigator. Subjects with only non-measurable disease at baseline will be part of the analysis and will be included in the numerator only if a CR was observed. Tumor assessments performed before the start of any further subsequent anti-cancer therapy will be considered in the assessment of BOR.

BOR is defined as the best response as recorded from randomization until documented objective disease progression using RECIST Version 1.1. BOR is derived from all time point responses observed while on study treatment and during the follow up period (but before the initiation of subsequent anti-cancer therapy [drug therapy, curative radiotherapy, curative surgery]). Each subject's BOR will be categorized as complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), or not evaluable (NE). To classify BOR as SD, there should be a qualifying SD assessment at least 8 weeks after randomisation. Subjects without baseline or post-baseline tumor assessments will be treated as NE for BOR.

The ORR will be summarized by treatment arm and the associated 95% CI will be estimated using the Clopper Pearson method on ITT populations. The ORR of Arm 1 will be compared to Arm 2 using a Cochran-Mantel-Haenszel test adjusting by randomisation stratification factors per IWRS and odds ratio (and its 95% CI) will be estimated using Mantel-Haenszel method. Sensitivity analysis will be repeated for PP populations.

The number and percent of subjects with their best overall response will be summarised by treatment arm.

The estimand of ORR is described in Table 5.

**Table 5 Secondary Efficacy Endpoint (ORR) in Estimand Framework**

| **Statistical category** | **Estimand:**<br>**Treatment:** Randomized Arm 1 (irinotecan liposome injection+oxaliplatin+5-FU/LV) or Arm 2 (nab-paclitaxel+gemcitabine).<br>**Population:** Subjects who have not previously received chemotherapy for metastatic adenocarcinoma of the pancreas as specified in the inclusion and exclusion criteria (Protocol Section 4.1 and Section 4.2), respectively.<br>**Endpoint (Variable)**: ORR, defined as the proportion of subjects with a BOR characterised as either a CR or PR per RECIST v1.1<br>**Intercurrent events:**<br>1. Start of subsequent anti-cancer therapy (drug therapy, curative radiotherapy, curative surgery) including new antineoplastic treatment<br>2. Permanently discontinuation from study treatment without documented disease progression | | |
|---|---|---|---|
| | **Analysis set** | **Intercurrent event handling strategy** | **Population-level summary (Analysis):** |
| Secondary | ITT | 1. Hypothetical strategy: Response assessments prior to ICE1 will be used. | Treatment comparison and odds ratio estimated using a Cochran-Mantel-Haenszel test |

<table>
<tr><td rowspan="2">Statistical category</td><td colspan="3">Estimand:<br>Treatment: Randomized Arm 1 (irinotecan liposome injection+oxaliplatin+5-FU/LV) or Arm 2 (nab-paclitaxel+gemcitabine).<br>Population: Subjects who have not previously received chemotherapy for metastatic adenocarcinoma of the pancreas as specified in the inclusion and exclusion criteria (Protocol Section 4.1 and Section 4.2), respectively.<br>Endpoint (Variable): ORR, defined as the proportion of subjects with a BOR characterised as either a CR or PR per RECIST v1.1<br>Intercurrent events:<br>1. Start of subsequent anti-cancer therapy (drug therapy, curative radiotherapy, curative surgery) including new antineoplastic treatment<br>2. Permanently discontinuation from study treatment without documented disease progression</td></tr>
<tr><td>Analysis set</td><td>Intercurrent event handling strategy</td><td>Population-level summary (Analysis):</td></tr>
<tr><td></td><td></td><td>2. Treatment policy strategy: ICE 2 will not affect the assessment of ORR.</td><td></td></tr>
<tr><td>Sensitivity</td><td>PP</td><td>As secondary</td><td>As secondary</td></tr>
</table>

Tumor assessment

Tumor assessment for target, non-target and new lesions, and overall response will be listed.

### *3.4.3 Exploratory Efficacy Endpoint Analysis*

#### *3.4.3.1 Patient-Reported Outcomes Analysis*

Analyses of quality of life is an exploratory analysis that will be carried out primarily on ITT. Analyses of QoL based on the PRO population may be used as the sensitivity analyses.

The instrument descriptions and scoring algorithms of EORTC QLQ-C30, QLQ-PAN26, EQ-5D-5L and PRO-CTCAE are detailed in Appendix B, D, E, and F respectively.

For all PRO assessments, baseline is defined as the last observed measurement prior to first drug administration at C1D1. Post-baseline value is defined as a measurement taken after the first administration of study drug. Change from baseline is defined as post-baseline value minus baseline value and will be calculated for each post-baseline assessment. Questionnaires EORTC QLQ-C30, QLQ-PAN26, EQ-5D-5L are planned to be collected at CXD1. PRO-CTCAE is planned to be collected at CXD1 and CXD15.

The principle for scoring is the same for all domains. Outcome scores are computed by standardizing the average of the items (i.e., a raw score) comprising the domain. A linear transformation of the raw score is computed such that scores range from 0 to 100. Details are provided in Appendix. Depending on the domain, a higher score represents a higher ("better") level of functioning, or a higher ("worse") level of symptoms. More specifically, a high score for a functional domain represents a high/healthy level of functioning and a high score for the GHS represents a high level of QoL, but a high score for a symptom domain/item represents a high level of symptomatology/problems. Note that the global health status domain is based on only the two specific HRQoL items and not the entire questionnaire. If ≥50% of the items of a domain are present for a timepoint then the score will be calculated using the average of all

items answered, otherwise the score will be set to missing. For single measures, if the item is missing the domain score is set to missing.

Change from baseline defined as post-baseline value minus baseline value will be calculated for each assessment. At each post-baseline assessment, the change in symptoms, functioning, or GHS from baseline will be calculated for each domain and each item.

Analysis Visit Window

For summaries of PRO data, assessments will be assigned to calculated visit windows (4 weeks per cycle, details in Study Protocol Table 5). The time windows will be exhaustive so that data recorded at any timepoint have the potential to be summarized. Inclusion within the visit window will be based on the actual date and not the intended date of the visit. The window for the visits following baseline will be constructed in such a way that the upper limit of the interval falls half-way between the two visits. If there is more than one value per patient within an assessment window then the closest to the planned study day value should be summarised, or the earlier in the event the values are equidistant from the planned study day. The value at a given timepoint will be missing if no assessment was reported within the specified assessment window around the planned study day.

All PRO instruments will be listed separately by treatment arm and subject.

Descriptive summary

EORTC QLQ-C30, QLQ-PAN26, and PRO-CTCAE results will be summarised at each visit by treatment arm using the number of subjects with non-missing data (n), mean, standard deviation, median, minimum and maximum. Change from baseline will be summarized using the same statistics. Change from baseline scores at each visit will be compared using an analysis of covariance (ANCOVA) model with treatment as a fixed effect and baseline as a covariate adjusting by randomisation stratification factors per IWRS. Least square mean, standard error and 95% CI of treatment difference will be presented.

EQ VAS and EQ-5D index value will be summarized and analyzed using the same method as above. Standard EQ-5D-5L value set from US will be applied to generate index value. EQ-5D-5L descriptive system will also be summarized by presenting the frequency and proportion of each level for each dimension by visit and by treatment arm.

The mean with standard error of above PRO scores over time will be plotted by visit and treatment arm.

Time to deterioration (TTD)

TTD will be defined as the duration of time from the date of randomization to the date of the first deterioration in PRO scores of at least one threshold unit as compared to the baseline score.

For subjects who experienced a firs deterioration, TTD will be computed as follows and then converted to months:

Time to deterioration on EORTC QLQ-C30 outcomes is calculated as follows:

TTD = (First Deterioration Date– Date of Randomisation + 1)/30.4375

where first deterioration date refers to the first time that the subject's domain/item score hit a threshold of 10 points or more worsening from their baseline score with no later improvement above this threshold observed during the course of the study. [Bonnetain, 2010]

Subjects who do not experience deterioration prior to the end of follow up or data cutoff date will be censored at the date of last available PRO assessment. Patients with no baseline assessment, and patients with no post-baseline assessments or with scores at baseline that are close to "floor" (GHS, Function scale

<20, Symptom scale >80) will be censored at the date of randomization. Death or disease progression will not be considered events.

Number and percent of subjects with deterioration and censored will be summarized by treatment arm.

Time to deterioration will be estimated by KM methodology. Treatment arms will be compared using stratified log rank test and the estimated HR from stratified Cox regression analysis will be presented to summarise the effect of Arm 1. Estimates of median time to deterioration and HR will be presented with corresponding 95% CIs. KM based rates of being alive without deterioration at 3, 6, 9, 12, and 18 months will be estimated and associated two-sided 95% CIs will be provided. The KM curves of the two treatment arms with HR will be plotted.

Stable, improved or worsened scores

Number and percent of subjects with improved (>=10% improvement vs baseline and remaining improved over baseline for >= 4 weeks ± 2 weeks), worsened (either died or had scores that worsened by 10% vs baseline), or stable (did not meet criteria for improved or worsened) QoL scores as assessed by QLQ-C30 will be summarized by visit and treatment arm. Differences in percentages between Arm 1 and Arm 2 will be provided with 95% CIs. The two treatment arms will be compared using a Cochran-Mantel-Haenszel test, adjusting by randomisation stratification factors per IWRS.

Notes:

- For those with multiple records on the same assessment date, the first one by time point and sequence number will be selected as scheduled assessment. All assessments will be included in the time-to-event analysis.
- For subjects who receive a subsequent anti-cancer therapy (drug therapy, curative radiotherapy, curative surgery), only PRO measurements before the initiation of subsequent therapy will be included in the analyses.

#### *3.4.3.2 Other Exploratory Efficacy Endpoint Analysis*

Time to Treatment Failure

TTF will be calculated as follows:

TTF (months) = (Event or Censoring Date – Date of Randomisation + 1)/30.4375

Subjects who do not have a treatment failure will be censored on the date of last contact.

The number and proportion of subjects of treatment failure in each treatment arm will be summarised. TTF will be estimated by KM methodology. Treatment arms will be compared using stratified log rank test and the estimated HR from stratified Cox regression analysis will be presented to summarise the effect of Arm 1. Estimates of median TTF and HR will be presented with corresponding 95% CIs.

Duration of Response

DOR will be calculated as follows:

DOR (months) = (Progression/Death/Censoring Date – Response Start Date + 1) / 30.4375

Subjects who do not have documented disease progression or death will be censored following the same rules as PFS specified in Table 3

For each treatment arm, the number of subjects with and without subsequent disease progression or death will be summarized. DOR will be analyzed using the same approach as TTF.

Time to Response

TTR will be computed only for subjects who achieved complete response or partial response.

TTR will be calculated as follows:

TTR (months) = (First response Start Date – Date of Randomisation + 1)/30.4375

TTR of each treatment arm will be summarized descriptively.

Genotyping: UGT1A1

The number and percentage of subjects in each UGT1A1*28 allele status (homozygous/other) and other UGT1A genotypes (if known) will be summarised. Analyses by UGT1A1*28 allele status (homozygous/other) are described in Sections 3.4.4, 3.5, and 3.6.1. UGT1A1 data will also be listed in subject-level data listing.

Biomarkers CA 19-9

The biomarker CA 19-9 concentration will be summarised descriptively by treatment arm. CA 19-9 data will also be listed in subject-level data listing.

Biobanking

The exploratory endpoint comprises biobanking of samples for future analysis, among subjects who consent. Analysis of biobank samples will be performed outside the scope of the main study and reported separately.

### *3.4.4 Subgroups*

Subgroup analyses will be performed to explore the consistency of the treatment effect for subgroups. Descriptive statistics of primary and key secondary endpoints (OS, PFS and ORR) will be provided within each category of the following variables:

- presence of liver metastases at baseline (yes, no)
- number of metastatic sites (0, 1, 2, ≥3)
- baseline ECOG performance status (0/1)
- region (North America/East Asia/Rest of the World)
- main pancreatic tumour location (head, other)
- baseline CA 19-9 (<37 U/mL, ≥37 U/mL)
- race (Asian, American Indian or Alaska Native, Black or African American, Native Hawaiian or Other Pacific Islander, White, not reported, Other)
- sex (male, female)
- age (<65 years, >=65 years)
- UGT1A1*28 allele status (homozygous/non-homozygous).

If a level of a factor consists of fewer than 5% of randomized subjects, analysis within that level will be omitted.

Analyses will be done within subgroup. Estimated HRs and CIs for OS and PFS and odds ratios and CIs for ORR within subgroup analyses will be presented as a forest plot.

Other subgroup analyses may be performed as deemed appropriate. If any safety analyses identify important imbalances between arms, subgroup analyses of these endpoints (OS, PFS and ORR) may be performed.

## 3.5 Pharmacokinetic Assessment

Listings, Figures and Summary Statistics of Concentrations

PK assessments will be performed for Arm 1 only. Individual plasma concentrations for total irinotecan, SN-38, 5-FU, and oxaliplatin will be listed and summarised by timepoint and dose level using descriptive statistics for continuous variables (number of available observations, mean, median, SD, minimum, maximum, geometric mean and geometric coefficient of variation assuming log-normally distributed data) on PK population. When applicable, the descriptive statistics should be displayed by visit/time point, only if at least 2/3 (two thirds) of the data are above the limit of quantification (LoQ). Otherwise, only minimum and maximum will be reported. As a standard rule, PK concentration should be displayed with the same precision as the LoQ. In descriptive statistics, calculations derived from PK concentrations (mean, min, max, median, SD, etc) should follow the same rule whereas coefficient of variation (CV%) will only be displayed with one decimal digit only.

Linear and semilogarithmic plots of individual and mean plasma concentration-time profiles of total irinotecan, SN-38 and oxaliplatin as well as spaghetti plots will be reported.

A full description of the bioanalytical methods used and bioanalysis results obtained of the plasma concentrations will be described in a separate standalone bioanalytical report.

Pharmacokinetic Data Analysis

Pharmacokinetics of total irinotecan and SN-38 will be quantified from the concentrations from plasma samples using nonlinear mixed effect modeling (NONMEM). The initial PK analysis will use the empirical Bayesian estimation; however, additional covariate analyses will be performed to evaluate alternative baseline factors specific to PDAC. The resulting PK estimates will be used to evaluate the association between PK and pharmacodynamics (efficacy and safety endpoints).

Oxaliplatin and/or 5-FU concentrations might be used for further PK characterisation if more investigations are required.

A full description of the pharmacokinetic analysis of the concentration data will be captured separately in a data analysis plan, and PK results will be reported in a standalone report.

Pharmacokinetics/Pharmacodynamics Relationship

Graphical exploration will be performed to investigate any relationship between PK and pharmacodynamic endpoints (efficacy, safety). If a trend is shown, PK/PD modelling will be performed and this will be described in a separate Data Analysis Plan and reported in a standalone report.

Genotyping: UGT1A1 and Pharmacokinetics

The impact of UGT1A1*28 allele status on pharmacokinetic profile of subjects treated with irinotecan liposome injection+oxaliplatin+5-FU/LV will be evaluated.

Detailed description of this assessment will be included in the standalone pharmacokinetic report.

## 3.6 Safety Analysis

All safety data will be included in the subject data listings. Analyses and summary tables will be based upon the safety population.

### *3.6.1 Adverse Events*

1. An overall summary table of all adverse events will be presented, which will summarize the number and percentages of subjects and number of events of the following categories:
    - AEs,
    - TEAEs,
    - NCI CTCAE grade 3/4/5 TEAEs,
    - Serious TEAEs,
    - Serious TEAEs due to COVID-19
    - TEAEs leading to discontinuation of any Investigational Medicinal Product (IMP),
    - TEAEs leading to discontinuation of Irinotecan liposome injection,
    - TEAEs leading to dose reduction of any IMP,
    - TEAEs leading to dose reduction of Irinotecan liposome injection,
    - TEAEs leading to dose interruption of any IMP,
    - TEAEs leading to dose interruption of Irinotecan liposome injection, and
    - TEAEs leading to death.

All the above events (except for regular AEs) related to any IMP or Irinotecan liposome injection will be summarized respectively. TEAEs leading to death due to COVID-19 will be summarized.

2. The number, percentage of subjects and frequency of the following TEAEs will be summarized by SOC, PT, CTCAE grade (Any Grade, Grade 3-4) and by treatment arm and overall.
    - TEAEs
        - Related to any IMP
        - Related to Irinotecan liposome injection
    - Serious TEAEs
        - Related to any IMP
        - Related to Irinotecan liposome injection
    - TEAEs leading to discontinuation of any IMP
        - Related to any IMP
        - Related to Irinotecan liposome injection
    - TEAEs leading to discontinuation of Irinotecan liposome injection
        - Related to Irinotecan liposome injection

- TEAEs leading to dose reduction of any IMP
- TEAEs leading to dose reduction of Irinotecan liposome injection
- TEAEs leading to dose interruption of any IMP
- TEAEs leading to dose interruption of Irinotecan liposome injection
- TEAEs leading to death
  - Related to any IMP
  - Related to Irinotecan liposome injection
- Treatment-emergent AESIs

3. The number, percentage of subjects and frequency of the following TEAEs will be summarized by SOC, PT, UGT1A1*28 Allele Status (homozygous/other), and by treatment arm and overall.
   - TEAEs
     - Related to Irinotecan liposome injection
   - NCI CTCAE grade 3/4/5 TEAEs related to Irinotecan liposome injection
   - Serious TEAEs related to Irinotecan liposome injection
   - TEAEs leading to discontinuation of study treatment related to Irinotecan liposome injection
   - TEAEs leading to death
     - Related to any IMP
     - Related to Irinotecan liposome injection
4. The number, percentage of subjects and frequency of the following TEAEs will be summarized by SOC, preferred term (PT), age (<65 years, >=65 years), race, gender and by treatment arm and overall.
   - TEAEs
   - TEAEs leading to death

   Overall summary of TEAEs will also be present by age, race, gender and by treatment arm and overall.
5. Listings of following AEs will be presented by subject, SOC and PT. All TEAEs will be flagged in the listings.
   - AEs
   - NCI CTCAE grade 3/4/5 TEAEs
   - SAEs
   - SAEs due to COVID-19
   - AEs leading to discontinuation of any IMP
   - AEs leading to discontinuation of Irinotecan liposome injection, Oxaliplatin, Leucovorin, 5-FU, Nab-paclitaxel or Gemcitabine respectively

- AEs leading to dose reduction of Irinotecan liposome injection, Oxaliplatin, Leucovorin, 5-FU, Nab-paclitaxel or Gemcitabine respectively
- AEs leading to dose interruption of Irinotecan liposome injection, Oxaliplatin, Leucovorin, 5-FU, Nab-paclitaxel or Gemcitabine respectively
- AEs leading to death
- AESIs

All COVID-19 cases (suspected or confirmed) should be considered as SAEs. AE due to COVID-19 is derived per COVID-19 SMQ list.

### *3.6.2 Death*

The number, percentage of subjects who died (any death, TEAE, treatment related TEAE), and primary reason for death (any death) will be summarized by treatment arm.

All deaths on study will be listed along with the primary reason for death. For those deaths attributed to TEAE, the tables and listings will be presented per Section 3.6.1.

### *3.6.3 Clinical Laboratory Tests*

Hematological and biochemistry toxicities when available will be recorded and graded according to the NCI-CTC criteria, version 5.0.

Descriptive statistics will be provided for selected clinical laboratory test results (haematology and chemistry) and changes from baseline for the minimum post-baseline value, maximum post-baseline value, and last post-baseline value.

Directional shifts in laboratory toxicity grades (comparing baseline grade with worst post-baseline grade) will be analyzed using standard shift tables, presenting number and proportion of subjects and their maximum grade shift for selected laboratory parameters (ALT, AST, total bilirubin, ALP, creatinine, hemoglobin, absolute neutrophils, platelet counts, white blood cell counts, aPTT, and INR). Individual line plots over time will also be presented for these selected laboratory parameters.

The number and percentage of subjects with the following potentially clinically significant abnormal liver function tests at any post-Baseline visits will be summarized:

- ALT ≥3xULN to <5xULN, ≥5xULN to <10xULN, ≥10xULN to <20xULN, and ≥20xULN
- AST ≥3xULN to <5xULN, ≥5xULN to <10xULN, ≥10xULN to <20xULN, and ≥20xULN
- Total bilirubin ≥2xULN
- ALT or AST ≥3×ULN with total bilirubin ≥2×ULN without elevation of ALP (< 2xULN)
- ALT or AST ≥3xULN, total bilirubin ≥2xULN, and ALP ≥2xULN

The same summary will also be repeated by presence of liver metastases at baseline (yes, no).

Number of subjects for selected laboratory parameters with a difference ≥ 5% for CTCAE grade 1-4 toxicity or ≥ 2% for grade 3-4 toxicity between treatment groups will be summarized.

Chemistry

- Albumin Decrease
- Calcium Decrease

- Phosphate Decrease
- Potassium Decrease
- Sodium Decrease
- Alanine Aminotransferase Increase
- Alkaline Phosphatase Increase
- Aspartate Aminotransferase Increase
- Bilirubin Increase
- Calcium Increase
- Creatinine Increase
- Potassium Increase

Hematology

- Hemoglobin Decrease
- Lymphocyte Count Decrease
- Neutrophil Count Decrease
- Platelet Count Decrease
- Leukocytes Count decrease

Standard International (SI) units will be used in the descriptive summary tables.

- When both central and local results from the same sampling date are available or only central is available but local is missing, central results will be used.
- When central is missing but local results from the same sampling date is available, local results will be used.
- For those with multiple results from central lab on the same sampling date, the first one by time point will be used.

Listings of hematological and biochemistry will list both central and local lab results in Standard International units and local units and sort by test, date and time. Local lab will be flagged. Additionally, listings of urinalysis (dipstick) and dihydropyrimidine dehydrogenase (DPD) deficiency testing will be provided.

### *3.6.4 Pregnancy Test*

Urine or serum pregnancy test will be listed.

### *3.6.5 Electrocardiograms*

Number and percentage of subjects with QTcF intervals in the categories below will be provided.

- Post-baseline absolute QTcF interval >450 msec,
- Post-baseline absolute QTcF interval >480 msec,
- Post-baseline absolute QTcF interval >500 msec.
- Change from baseline QTcF interval increase >30 msec,

- Change from baseline QTcF interval increase >60 msec.

For continuous ECG parameters (heart rate, RR interval, PR interval, QRS duration, QT interval, QTcF interval), summary statistics will be presented for baseline and changes from baseline for the minimum post-baseline value, maximum post-baseline value and last post-baseline value.

For interpretation of clinical significance (normal / abnormal, not clinically significant / abnormal, clinically significant / not evaluable), a frequency table will be presented at baseline and the worst post-baseline assessment.

ECG data will be listed at each assessment.

### *3.6.6 Vital Signs*

Summary statistics will be presented for baseline and changes from baseline for the minimum post-baseline value, maximum post-baseline value and last post-baseline value.

Vital signs will be listed at each assessment.

### *3.6.7 Physical Examinations*

For interpretation of clinical significance (normal / abnormal, not clinically significant / abnormal, clinically significant / not evaluable), a frequency table will be presented at baseline and post-baseline assessment.

### *3.6.8 ECOG Performance Status*

The frequency and percentage of subjects with each performance status score will be displayed by visit. A shift table presenting the shift from baseline to worst post-baseline score will also be presented. ECOG data will also be listed in subject-level data listing.

### *3.6.9 Other Data*

Hospitalization data will be listed.

# 4 INDEPENDENT DATA MONITORING BOARD AND INTERIM ANALYSIS

An IDMC will be established for this study to operate as an independent expert advisory group with the responsibility of evaluating cumulative safety and other clinical trial data at regular intervals. As such, the primary objective of the IDMC is to monitor the safety of the subjects enroled in the study by reviewing the available clinical data at scheduled time points as well as on an ad hoc basis, as needed. Items reviewed will include (but not limited to) safety events, any available results of PK testing, and UGT1A1*28 allele status (homozygous/other). Attention will be paid to determining whether any study procedure needs to be modified for subjects who are homozygous for the UGT1A1*28 allele.

The same IDMC will evaluate also the efficacy data as well as the safety data at the time of the interim analysis. The IDMC will be responsible for reviewing the futility and efficacy results in the interim analysis and making appropriate recommendations based on those results.

The planned frequency of the IDMC is planned to be as follows and will be agreed with the IDMC experts:

After the 50th randomised subject has been followed for at least 28 days (follow-up timeframe equivalent of one cycle)

- Every 6 months and additionally timed with each planned interim analysis:
  - Interim analysis for futility and efficacy (no less than 50% of the planned final number of OS events in ITT population i.e. 272 of 543)

At the time of interim analysis, analyses provided to the IDMC will include:

- the boundary values for significance,
- for OS and PFS,
  - the p-value from a stratified log rank test comparing the two treatment arms, stratified by the randomisation stratification factors,
  - an estimate of the HR between the two arms based on a Cox proportional hazards model, stratified by the randomisation stratification factors, and
  - median survival time and its 95% CIs KM analysis by treatment arm.
  - Number and type of events and Number of subjects censored by type of censoring by treatment arm
- for ORR,
  - the p-value from a Cochran-Mantel-Haenszel test comparing the two treatment arms, adjusting by randomisation stratification factors, and
  - proportion of ORR and associated 95% CI will be estimated using the Clopper Pearson method by treatment arm
  - Number and percent of subjects with their best overall response by treatment arm

Details are documented in the separate IDMC charter.

In order to maintain the scientific integrity of this trial, access to by treatment arm study data will be strictly controlled prior to the interim and final analyses. During this time, analyses using actual treatment codes will be performed only at the interim analysis points and IDMC data review specified in the protocol/SAP. For those safety and efficacy analyses assigned to the IDMC, only the designed independent statistical team, will perform the by treatment arm analyses.

Data sets will be created for the purpose of aggregate data review by the sponsor in which treatment assignment is scrambled so that personnel involved in the day-to-day conduct of the trial and development and validation of analysis programs will be blinded to subject treatment assignment.

# 5 CHANGES FROM PROTOCOL-SPECIFIED STATISTICAL ANALYSES

The following updates in the SAP not in protocol version 5 dated 19 August 2021.

- Change time to deterioration exploratory objective only includes GHS, function domains, and disease related symptoms from EORTC QLQ-C30Change analysis day calculation from using first dose of study treatment to randomization
- Disposition includes subjects who received non-planned study treatments and subjects with ongoing long-term follow up
- Change OS sensitivity analysis Wilcoxon analysis to Unstratified log rank
- Clarify new anti-cancer therapy to subsequent anti-cancer therapy (drug therapy, curative radiotherapy, curative surgery) including new antineoplastic treatment.
- Clarify analysis Intent-to-Treat definition from all randomised subjects who have given their informed consent to all randomised subjects to whom study treatment has been assigned by

randomization. Subjects will be analyzed according to the assigned treatment per randomization procedure.

- Clarify Safety Population is a subset of the ITT population that received at least one dose (including a partial dose) of any component of the study medication in the combination therapy). Subjects will be analyzed according to the actual received treatment
- Remove sensitivity analysis of OS using Cox regression with stepwise selection and univariate analysis of OS for prognostic factors
- Change analyses of QoL primarily based on ITT population. PRO population may be used as the sensitivity analyses

# 6 PROGRAMMING SPECIFICATIONS

Analyses will be performed using SAS® version 9.3 or higher. All available data will be presented in subject data listings which will be sorted by subject and visit date as applicable. Detailed Programming Specifications will be provided in a separate document.

# APPENDIX A: REFERENCES

Common Terminology Criteria for Adverse Events (CTCAE) v5.0. November 27, 2017. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

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(2):228–47.

EORTC QLQ-C30 Manual, (third edition), Brussels, 2001.

Glimm E, Maurer W, Bretz F. Hierarchical testing of multiple endpoints in group-sequential trials. Stat Med 2010;29(2):219-28.

Hwang IK, Shih WJ, De Cani JS. Group sequential designs using a family of type I error probability spending functions. Stat Med 1990;9:1439-45.

Bonnetain F, Dahan L, Maillard E, et al. Time until definitive quality of life score deterioration as a means of longitudinal analysis for treatment trials in patients with metastatic pancreatic adenocarcinoma. Eur J Cancer. 2010;46:2753-2762.

# APPENDIX B: NCI PRO-CTCAE ITEMS

PRO-CTCAE (version 1.0) is PRO measure of the frequency, severity and/or interference of symptoms experienced by patients participating in cancer clinical trials. A subset of items relevant to this study are selected.

The full instrument can be found at https://healthcaredelivery.cancer.gov/pro-ctcae/instrument-pro.html .

## NCI PRO-CTCAE™ ITEMS

**Item Library Version 1.0**
**English**
**Form created on 21 November 2019**

**As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please check or mark an ☒ in the one box that best describes your experiences over the past 7 days...**

| | | | | | |
|---|---|---|---|---|---|
| 1. | In the last 7 days, what was the SEVERITY of your MOUTH OR THROAT SORES at their WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |
| | In the last 7 days, how much did MOUTH OR THROAT SORES INTERFERE with your usual or daily activities? | | | | |
| | ○ Not at all | ○ A little bit | ○ Somewhat | ○ Quite a bit | ○ Very much |
| 2. | In the last 7 days, what was the SEVERITY of SKIN CRACKING AT THE CORNERS OF YOUR MOUTH at its WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |
| 3. | In the last 7 days, what was the SEVERITY of your PROBLEMS WITH TASTING FOOD OR DRINK at their WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |
| 4. | In the last 7 days, what was the SEVERITY of your DECREASED APPETITE at its WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |
| | In the last 7 days, how much did DECREASED APPETITE INTERFERE with your usual or daily activities? | | | | |
| | ○ Not at all | ○ A little bit | ○ Somewhat | ○ Quite a bit | ○ Very much |
| 5. | In the last 7 days, how OFTEN did you have NAUSEA? | | | | |
| | ○ Never | ○ Rarely | ○ Occasionally | ○ Frequently | ○ Almost con-stantly |
| | In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |

# NCI PRO-CTCAE™ ITEMS

**Item Library Version 1.0**
**English**
**Form created on 21 November 2019**

| | | | | | |
|---|---|---|---|---|---|
| 6. | In the last 7 days, how OFTEN did you have VOMITING? | | | | |
| | ○ Never | ○ Rarely | ○ Occasionally | ○ Frequently | ○ Almost constantly |
| | In the last 7 days, what was the SEVERITY of your VOMITING at its WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |

| | | |
|---|---|---|
| 7. | In the last 7 days, did you have any INCREASED PASSING OF GAS (FLATULENCE)? | |
| | ○ Yes | ○ No |

| | | | | | |
|---|---|---|---|---|---|
| 8. | In the last 7 days, how OFTEN did you have BLOATING OF THE ABDOMEN (BELLY)? | | | | |
| | ○ Never | ○ Rarely | ○ Occasionally | ○ Frequently | ○ Almost constantly |
| | In the last 7 days, what was the SEVERITY of your BLOATING OF THE ABDOMEN (BELLY) at its WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |

| | | | | | |
|---|---|---|---|---|---|
| 9. | In the last 7 days, what was the SEVERITY of your CONSTIPATION at its WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |

| | | | | | |
|---|---|---|---|---|---|
| 10. | In the last 7 days, how OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA/DIARRHOEA)? | | | | |
| | ○ Never | ○ Rarely | ○ Occasionally | ○ Frequently | ○ Almost constantly |

| | | | | | |
|---|---|---|---|---|---|
| 11. | In the last 7 days, how OFTEN did you have PAIN IN THE ABDOMEN (BELLY AREA)? | | | | |
| | ○ Never | ○ Rarely | ○ Occasionally | ○ Frequently | ○ Almost constantly |
| | In the last 7 days, what was the SEVERITY of your PAIN IN THE ABDOMEN (BELLY AREA) at its WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |
| | In the last 7 days, how much did PAIN IN THE ABDOMEN (BELLY AREA) INTERFERE with your usual or daily activities? | | | | |
| | ○ Not at all | ○ A little bit | ○ Somewhat | ○ Quite a bit | ○ Very much |

# NCI PRO-CTCAE™ ITEMS

**Item Library Version 1.0**
**English**
**Form created on 21 November 2019**

| | | | | | |
|---|---|---|---|---|---|
| 12. | In the last 7 days, what was the SEVERITY of your SHORTNESS OF BREATH at its WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |
| | In the last 7 days, how much did your SHORTNESS OF BREATH INTERFERE with your usual or daily activities? | | | | |
| | ○ Not at all | ○ A little bit | ○ Somewhat | ○ Quite a bit | ○ Very much |

| | | | | | |
|---|---|---|---|---|---|
| 13. | In the last 7 days, what was the SEVERITY of your COUGH at its WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |
| | In the last 7 days, how much did COUGH INTERFERE with your usual or daily activities? | | | | |
| | ○ Not at all | ○ A little bit | ○ Somewhat | ○ Quite a bit | ○ Very much |

| | | |
|---|---|---|
| 14. | In the last 7 days, did you have any RASH? | |
| | ○ Yes | ○ No |

| | | | | | |
|---|---|---|---|---|---|
| 15. | In the last 7 days, did you have any HAIR LOSS? | | | | |
| | ○ Not at all | ○ A little bit | ○ Somewhat | ○ Quite a bit | ○ Very much |

| | | | | | |
|---|---|---|---|---|---|
| 16. | In the last 7 days, what was the SEVERITY of your HAND-FOOT SYNDROME (A RASH OF THE HANDS OR FEET THAT CAN CAUSE CRACKING, PEELING, REDNESS OR PAIN) at its WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |

| | | | | | |
|---|---|---|---|---|---|
| 17. | In the last 7 days, what was the SEVERITY of your NUMBNESS OR TINGLING IN YOUR HANDS OR FEET at its WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |
| | In the last 7 days, how much did NUMBNESS OR TINGLING IN YOUR HANDS OR FEET INTERFERE with your usual or daily activities? | | | | |
| | ○ Not at all | ○ A little bit | ○ Somewhat | ○ Quite a bit | ○ Very much |

# NCI PRO-CTCAE™ ITEMS

**Item Library Version 1.0**
**English**
**Form created on 21 November 2019**

| | | | | | |
|---|---|---|---|---|---|
| 18. | In the last 7 days, how OFTEN did you have ACHING MUSCLES? | | | | |
| | ○ Never | ○ Rarely | ○ Occasionally | ○ Frequently | ○ Almost constantly |
| | In the last 7 days, what was the SEVERITY of your ACHING MUSCLES at their WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |
| | In the last 7 days, how much did ACHING MUSCLES INTERFERE with your usual or daily activities? | | | | |
| | ○ Not at all | ○ A little bit | ○ Somewhat | ○ Quite a bit | ○ Very much |

| | | | | | |
|---|---|---|---|---|---|
| 19. | In the last 7 days, how OFTEN did you have ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS)? | | | | |
| | ○ Never | ○ Rarely | ○ Occasionally | ○ Frequently | ○ Almost constantly |
| | In the last 7 days, what was the SEVERITY of your ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS) at their WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |
| | In the last 7 days, how much did ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS) INTERFERE with your usual or daily activities? | | | | |
| | ○ Not at all | ○ A little bit | ○ Somewhat | ○ Quite a bit | ○ Very much |

| | | | | | |
|---|---|---|---|---|---|
| 20. | In the last 7 days, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |
| | In the last 7 days, how much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE with your usual or daily activities? | | | | |
| | ○ Not at all | ○ A little bit | ○ Somewhat | ○ Quite a bit | ○ Very much |

# NCI PRO-CTCAE™ ITEMS

**Item Library Version 1.0**
**English**
**Form created on 21 November 2019**

| Do you have any other symptoms that you wish to report? | |
|---|---|
| ○ Yes | ○ No |

Please list any other symptoms:

| | | | | | |
|---|---|---|---|---|---|
| 1. | In the last 7 days, what was the SEVERITY of this symptom at its WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |
| 2. | In the last 7 days, what was the SEVERITY of this symptom at its WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |
| 3. | In the last 7 days, what was the SEVERITY of this symptom at its WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |
| 4. | In the last 7 days, what was the SEVERITY of this symptom at its WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |
| 5. | In the last 7 days, what was the SEVERITY of this symptom at its WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |

# APPENDIX C: PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings.

**Algorithm for Treatment Emergence of Adverse Events:**

| START DATE | STOP DATE | ACTION |
|---|---|---|
| Known | Known | If start date time< study med start date time, then not TEAE<br>If start date time >= study med start date time, then TEAE |
| | Partial | If start date time < study med start date time, then not TEAE<br>If start date time >= study med start date time, then TEAE |
| | Missing | If start date time < study med start date time, then not TEAE<br>If start date time >= study med start date time, then TEAE |
| | | |
| Partial, but known components show that it cannot be on or after study med start date time | Known | Not TEAE |
| | Partial | Not TEAE |
| | Missing | Not TEAE |
| | | |
| Partial, could be on or after study med start date time | Known | If stop date time < study med start date time, then not TEAE<br>If stop date time >= study med start date time, then TEAE |
| | Partial | Impute stop date time as latest possible date (i.e. last day of month if day unknown or 31st December 23:59 if day and month are unknown), then:<br>If stop date time < study med start date time, then not TEAE<br>If stop date time >= study med start date time, then TEAE |
| | Missing | Assumed TEAE |
| | | |
| Missing | Known | If stop date time < study med start date time, then not TEAE<br>If stop date time >= study med start date time, then TEAE |
| | Partial | Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December 23:59 if day and month are unknown), then:<br>If stop date time < study med start date time, then not TEAE<br>If stop date time >= study med start date time, then TEAE |
| | Missing | Assumed TEAE |

**Algorithm for Prior / Concomitant Medications:**

| START DATE | STOP DATE | ACTION |
|---|---|---|
| Known | Known | If stop date time < study med start date time, assign as prior<br>If stop date time >= study med start date time and start date time <= end of treatment, assign as concomitant<br>If stop date time >= study med start date time and start date time > end of treatment, assign as post study |
| | Partial | Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December 23:59 if day and month are unknown), then:<br>If stop date time < study med start date time, assign as prior<br>If stop date time >= study med start date and start date time <= end of treatment, assign as concomitant<br>If stop date time >= study med start date and start date time > end of treatment, assign as post treatment |
| | Missing | If stop date is missing could never be assumed a prior medication<br>If start date time <= end of treatment, assign as concomitant<br>If start date time > end of treatment, assign as post treatment |
| | | |
| Partial | Known | Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January 00:01 if day and month are unknown), then:<br>If stop date time < study med start date time, assign as prior<br>If stop date time >= study med start date time and start date time <= end of treatment, assign as concomitant<br>If stop date time >= study med start date time and start date time > end of treatment, assign as post treatment |
| | Partial | Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December 00:01 if day and month are unknown), then:<br>If stop date time < study med start date time, assign as prior<br>If stop date time >= study med start date time and start date time <= end of treatment, assign as concomitant<br>If stop date time >= study med start date time and start date time > end of treatment, assign as post treatment |
| | Missing | Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January 00:01 if day and month are unknown), then:<br>If stop date is missing could never be assumed a prior medication<br>If start date time <= end of treatment, assign as concomitant<br>If start date time > end of treatment, assign as post treatment |
| | | |
| Missing | Known | If stop date time < study med start date time, assign as prior<br>If stop date time >= study med start date time, assign as concomitant<br>Cannot be assigned as 'post treatment' |
| | Partial | Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December 23:59 if day and month are unknown), then:<br>If stop date time < study med start date time, assign as prior<br>If stop date time >= study med start date time, assign as concomitant<br>Cannot be assigned as 'post treatment' |
| | Missing | Assign as concomitant |

# APPENDIX D: EORTC QLQ - C30 (V3.0)

## EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

Your birthdate (Day, Month, Year): ⌊ ⌋⌊ ⌋ ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

Today's date (Day, Month, Year): 31 ⌊ ⌋⌊ ⌋ ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

| | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|
| 1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase? | 1 | 2 | 3 | 4 |
| 2. Do you have any trouble taking a long walk? | 1 | 2 | 3 | 4 |
| 3. Do you have any trouble taking a short walk outside of the house? | 1 | 2 | 3 | 4 |
| 4. Do you need to stay in bed or a chair during the day? | 1 | 2 | 3 | 4 |
| 5. Do you need help with eating, dressing, washing yourself or using the toilet? | 1 | 2 | 3 | 4 |

| During the past week: | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|
| 6. Were you limited in doing either your work or other daily activities? | 1 | 2 | 3 | 4 |
| 7. Were you limited in pursuing your hobbies or other leisure time activities? | 1 | 2 | 3 | 4 |
| 8. Were you short of breath? | 1 | 2 | 3 | 4 |
| 9. Have you had pain? | 1 | 2 | 3 | 4 |
| 10. Did you need to rest? | 1 | 2 | 3 | 4 |
| 11. Have you had trouble sleeping? | 1 | 2 | 3 | 4 |
| 12. Have you felt weak? | 1 | 2 | 3 | 4 |
| 13. Have you lacked appetite? | 1 | 2 | 3 | 4 |
| 14. Have you felt nauseated? | 1 | 2 | 3 | 4 |
| 15. Have you vomited? | 1 | 2 | 3 | 4 |
| 16. Have you been constipated? | 1 | 2 | 3 | 4 |

| During the past week: | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|
| 17. Have you had diarrhea? | 1 | 2 | 3 | 4 |
| 18. Were you tired? | 1 | 2 | 3 | 4 |
| 19. Did pain interfere with your daily activities? | 1 | 2 | 3 | 4 |
| 20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television? | 1 | 2 | 3 | 4 |
| 21. Did you feel tense? | 1 | 2 | 3 | 4 |
| 22. Did you worry? | 1 | 2 | 3 | 4 |
| 23. Did you feel irritable? | 1 | 2 | 3 | 4 |
| 24. Did you feel depressed? | 1 | 2 | 3 | 4 |
| 25. Have you had difficulty remembering things? | 1 | 2 | 3 | 4 |
| 26. Has your physical condition or medical treatment interfered with your family life? | 1 | 2 | 3 | 4 |
| 27. Has your physical condition or medical treatment interfered with your social activities? | 1 | 2 | 3 | 4 |
| 28. Has your physical condition or medical treatment caused you financial difficulties? | 1 | 2 | 3 | 4 |

**For the following questions please circle the number between 1 and 7 that best applies to you**

29. How would you rate your overall health during the past week?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Very poor | | | | | | Excellent |

30. How would you rate your overall quality of life during the past week?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Very poor | | | | | | Excellent |



The EORTC QLQ-C30 (version 3) is a generic questionnaire that has been developed and validated to assess the QoL of cancer patients.

The PRO measure contains 30 items that measure health-related quality of life in patients with cancer. It includes a total of 30 items and is composed of scales that evaluate physical (five items), emotional (four items), role (two items), cognitive (two items), and social (two items) functioning, as well as global health

status (two items). There are also three symptom scales measuring nausea and vomiting (two items), fatigue (three items), and pain (two items), and six single items assessing financial impact and various physical symptoms, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties.

The items are based on 4-point (1 and 4 indicating 'not at all' and 'very much', respectively) and 7-point Likert scales (1 and 7 indicating 'very poor' and 'excellent', respectively).

The minimally significant mean change is 5 to 10 points on a scale of 0 to 100.

A high scale score represents a higher response level. Thus a high score for a functional scale represents a high / healthy level of functioning, a high score for the global health status / QoL represents a high QoL, but a high score for a symptom scale / item represents a high level of symptomatology / problems.

All scoring information specific to the QLQ-C30 is presented in Table 6.

The principle for scoring these domains is the same in all cases:

1. Estimate the average of the items that contribute to the domain; this is the raw score.

2. Use a linear transformation to standardize the raw score, so that scores range from 0 to 100; a higher score represents a higher ("better") level of functioning, or a higher ("worse") level of symptoms.

The technical details are provided below.

If items $I_1$, $I_2$, ... $I_n$ are included in a domain, the procedure is as follows:

Calculate the raw score (RS) as follows: $RS=( I_1+I_2+ ... +I_n)/n$

Apply the linear transformation as follows:

Functional scales: $S = 1 – ((RS -1)/range)\times100$

Symptom scales / items: $S = (RS -1)/range\times100$

Global health status/QoL: $S = (RS -1)/range\times100$

where Range is the difference between the maximum possible value of RS and the minimum possible value. The EORTC-QLQ-C30 has been designed so that all items in any domain take the same range of values. Therefore, the range of RS equals the range of the item values (see Table 6).

If at least half the components of a domain are present, then the domain score will be calculated using the average of all items answered as the raw score; otherwise the score will be set to missing. For single measures, it the item is missing the domain score is set to missing.

**Table 6 QLQ-C30 Scales and Scoring Details**

| | Number of items | Item range* | Item numbers | Minimum Not Missing |
|---|---|---|---|---|
| **Global health status/QoL** | | | | |
| Global health status/QoL | 2 | 6 | 29, 30 | 1 |
| | | | | |
| **Functional scales** | | | | |
| Physical functioning | 5 | 3 | 1-5 | 3 |
| Role functioning | 2 | 3 | 6, 7 | 1 |
| Emotional functioning | 4 | 3 | 21-24 | 2 |
| Cognitive functioning | 2 | 3 | 20, 25 | 1 |
| Social functioning | 2 | 3 | 26, 27 | 1 |
| | | | | |
| **Symptom scales / items** | | | | |
| Fatigue | 3 | 3 | 10, 12, 18 | 2 |
| Nausea and vomiting | 2 | 3 | 14, 15 | 1 |
| Pain | 2 | 3 | 9, 19 | 1 |
| Dyspnea | 1 | 3 | 8 | NA |
| Insomnia | 1 | 3 | 11 | NA |
| Appetite loss | 1 | 3 | 13 | NA |
| Constipation | 1 | 3 | 16 | NA |
| Diarrhoea | 1 | 3 | 17 | NA |
| Financial difficulties | 1 | 3 | 28 | NA |

* *Item range* is the difference between the possible maximum and the minimum response to individual items; most items take values from 1 to 4, giving *range* = 3.

# APPENDIX E: EORTC QLQ - PAN26 (1999)

## EORTC QLQ - PAN26

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

| During the past week: | Not at all | A little | Quite a bit | Very much |
|---|---|---|---|---|
| 31. Have you had abdominal discomfort? | 1 | 2 | 3 | 4 |
| 32. Did you have a bloated feeling in your abdomen? | 1 | 2 | 3 | 4 |
| 33. Have you had back pain? | 1 | 2 | 3 | 4 |
| 34. Did you have pain during the night? | 1 | 2 | 3 | 4 |
| 35. Did you find it uncomfortable in certain positions (e.g. lying down)? | 1 | 2 | 3 | 4 |
| 36. Were you restricted in the types of food you can eat as a result of your disease or treatment? | 1 | 2 | 3 | 4 |
| 37. Were you restricted in the amounts of food you could eat as a result of your disease or treatment? | 1 | 2 | 3 | 4 |
| 38. Did food and drink taste different from usual? | 1 | 2 | 3 | 4 |
| 39. Have you had indigestion? | 1 | 2 | 3 | 4 |
| 40. Were you bothered by gas (flatulence)? | 1 | 2 | 3 | 4 |
| 41. Have you worried about your weight being too low? | 1 | 2 | 3 | 4 |
| 42. Did you feel weak in your arms and legs? | 1 | 2 | 3 | 4 |
| 43. Did you have a dry mouth? | 1 | 2 | 3 | 4 |
| 44. Have you had itching? | 1 | 2 | 3 | 4 |
| 45. To what extent was your skin yellow? | 1 | 2 | 3 | 4 |
| 46. Did you have frequent bowel movements? | 1 | 2 | 3 | 4 |
| 47. Did you feel the urge to move your bowels quickly? | 1 | 2 | 3 | 4 |
| 48. Have you felt physically less attractive as a result of your disease and treatment? | 1 | 2 | 3 | 4 |

| During the past week: | Not at all | A little | Quite a bit | Very much |
|---|---|---|---|---|
| 49. Have you been dissatisfied with your body? | 1 | 2 | 3 | 4 |
| 50. To what extent have you been troubled with side-effects from your treatment? | 1 | 2 | 3 | 4 |
| 51. Were you worried about your health in the future? | 1 | 2 | 3 | 4 |
| 52. Were you limited in planning activities, for example meeting friends, in advance? | 1 | 2 | 3 | 4 |
| 53. Have you received adequate support from your health care professionals? | 1 | 2 | 3 | 4 |
| 54. Has the information given about your physical condition and treatment been adequate? | 1 | 2 | 3 | 4 |
| 55. Have you felt less interest in sex? | 1 | 2 | 3 | 4 |
| 56. Have you felt less sexual enjoyment? | 1 | 2 | 3 | 4 |



The QLQ-PAN26 is a disease-specific module that complements the QLQ-C30 questionnaire to capture concepts that are specific to pancreatic cancer (all disease stages).

The EORTC QLQ-PAN26 uses 26 items to quantify pain, dietary changes, jaundice, altered bowel habit, emotional problems related to pancreatic cancer, and other symptoms including cachexia, indigestion, flatulence, dry mouth, and taste changes. The items are based on 4-piont Likert scale, 1 and 4 indicating 'not at all' and 'very much', respectively. The questionnaire consists of symptom scales such as pancreatic pain symptom scale (four items 31, 33, 34, 35), upper gastrointestinal symptom scale (two items 36, 37), jaundice scale (two items 44, 45), body image scale (two items 48, 49), altered bowel habit

scale (two items 46, 47), health satisfaction scale (two items 53, 54), sexuality scale (two items 55, 56) and 10 single items.

The scoring approach for the QLQ-PAN26 is identical in principle to that for the symptom scales / single items of the QLQ-C30. All scoring information specific to the QLQ-PAN26 is presented in Table 7.

Interpretation:

All of the scales and single item measures range in score from 0 to 100. A high score for the symptom scales and/or single items represents a high level of symptomatology or problems, whereas a high score for the functional scales represents a high level of functioning.

Principle for scoring

1) Raw score

For each multi-item scale, calculate the average of the corresponding items.

Raw Score = $RS=\{(I1+ I2+ \dots +In)\ n\}$

For each single-item measure, the score of the concerning item corresponds to the raw score.

Take into account that the scoring of questions 55 and 56 must be reversed prior to statistical analysis.

2) Linear Transformation

To obtain the Score S, standardize the raw score to a 0 – 100 range following the transformation:

Functional scales: S = 1 – ((RS −1)/range)×100

Symptom scales / items: S = (RS −1)/range×100

The same missing data handling rule as QLQ-C30 will be implemented.

**Table 7 QLQ-PAN26 Scales and Scoring Details**

| | Number of items | Item range* | Item numbers | Minimum Not Missing |
|---|---|---|---|---|
| **Symptom scales / items** | | | | |
| Pancreatic pain | 4 | 3 | 31, 33 - 35 | 1 |
| Bloating | 1 | 3 | 32 | 1 |
| Digestive symptoms | 2 | 3 | 36, 37 | 1 |
| Taste | 1 | 3 | 38 | NA |
| Indigestion | 1 | 3 | 39 | NA |
| Flatulence | 1 | 3 | 40 | NA |
| Weight loss | 1 | 3 | 41 | NA |
| Weakness arms and legs | 1 | 3 | 42 | NA |
| Dry mouth | 1 | 3 | 43 | NA |
| Hepatic symptoms | 2 | 3 | 44, 45 | 1 |
| Altered bowel habit | 2 | 3 | 46, 47 | 1 |
| Body image | 2 | 3 | 48, 49 | 1 |
| Troubled with side-effects | 1 | 3 | 50 | NA |
| Future Worries | 1 | 3 | 51 | NA |
| Planning of activities | 1 | 3 | 52 | NA |
| | | | | |
| **Functional scales** | | | | |
| Satisfaction with health care | 2 | 3 | 53, 54 | 1 |
| Sexuality | 2 | 3 | 55, 56 | 1 |

* *Item range* is the difference between the possible maximum and the minimum response to individual items; most items take values from 1 to 4, giving *range* = 3.

# APPENDIX F: EQ-5D-5L (PER USER GUIDE V3.0)

Under each heading, please tick the ONE box that best describes your health TODAY.

**MOBILITY**

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

**SELF-CARE**

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

**USUAL ACTIVITIES** (*e.g. work, study, housework, family or leisure activities*)

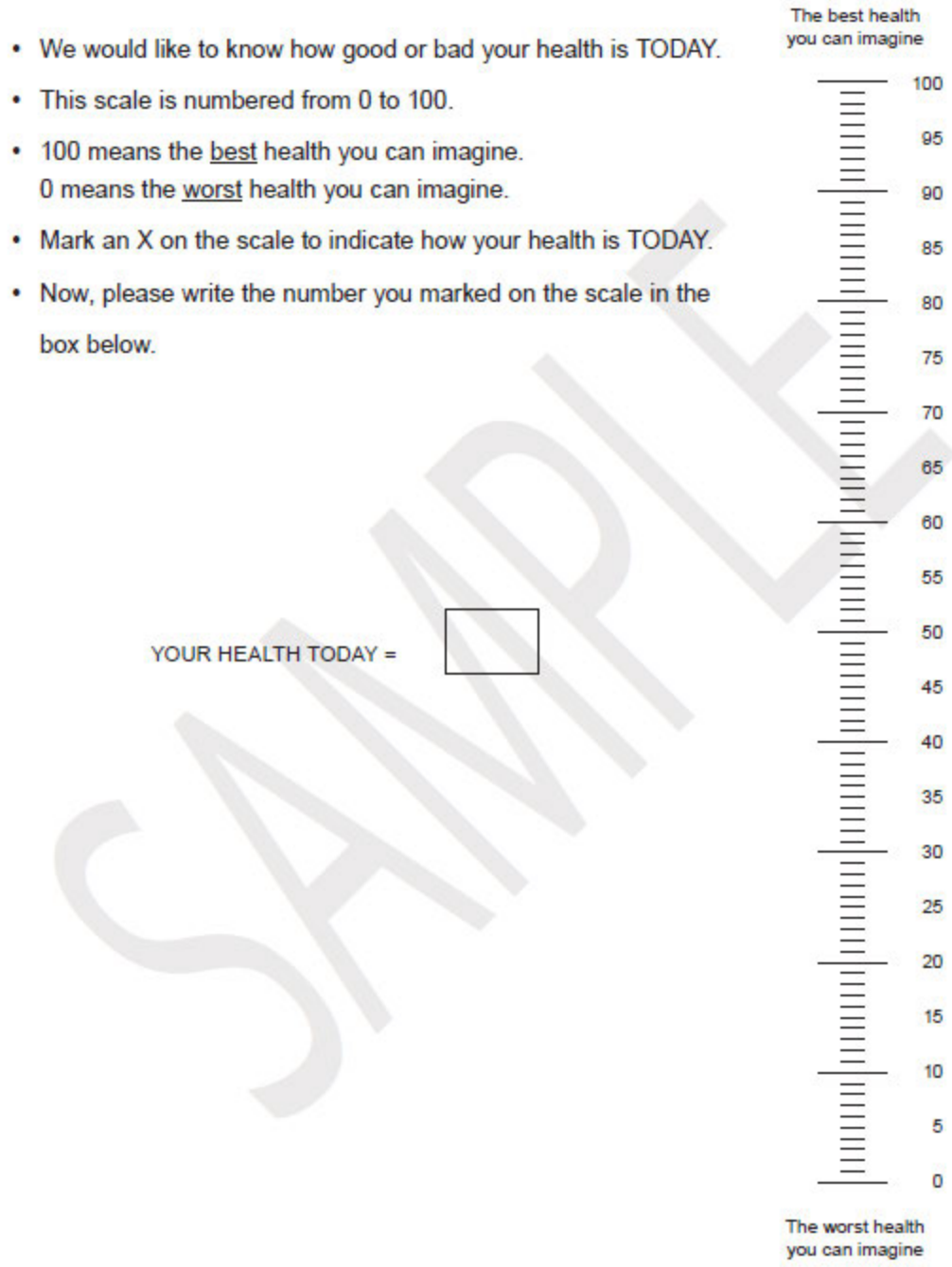
I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

**PAIN / DISCOMFORT**

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

**ANXIETY / DEPRESSION**

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑




EuroQol/EQ-5D is a standardized, reliable and validated instrument to measure quality of life. It consists of the EQ-5D descriptive system and the EQ Visual Analogue scale (EQ VAS).

The EQ-5D 5 level version (EQ-5D-5L) descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: level 1 (no problems), level 2 (slight problems), level 3 (moderate problems), level 4 (severe problems), and level 5 (extreme problems).

A total of 3125 health states are possible. Each state is referred to in terms of a 5-digit code. For example, state 11111 indicates no problem on any of the 5 dimensions, while state 12345 indicates no problems with mobility, slight problems with self-care, moderate problems with doing usual activities, severe pain or discomfort and extreme anxiety or depression. There should be only one response for each dimension and missing values will be coded as 9. If 2 levels are selected for a dimension, the dimension will be treated as missing.

The health state can be summarized to be a single number (5-digit code), or represented by a single summary number (index value), which reflects how good or bad a health state is according to the preferences of the general population of a country/region.

An EQ-5D summary index is derived by applying a formula that attaches values (weights) to each of the levels in each dimension. The index is calculated by deducting the appropriate weights from 1, the value for full health (i.e. state 11111). The collection of index values (weights) for all possible EQ-5D health states is called a value set. Most EQ-5D value sets have been obtained from a standardized valuation exercise, in which a representative sample of the general population in a country/region is asked to place a value on EQ-5D health states.

The EQ VAS records the subject's self-rated health state on a 100-point vertical, visual analogue scale (0 = worst imaginable health state; 100 = best imaginable health state).

# APPENDIX G: AJCC PROGNOSTIC STAGE GROUPS TABLE (8TH EDITION)

| When T is… | And N is… | And M is… | Then the stage group is… |
|---|---|---|---|
| Tis | N0 | M0 | 0 |
| T1 | N0 | M0 | IA |
| T1 | N1 | M0 | IIB |
| T1 | N2 | M0 | III |
| T2 | N0 | M0 | IB |
| T2 | N1 | M0 | IIB |
| T2 | N2 | M0 | III |
| T3 | N0 | M0 | IIA |
| T3 | N1 | M0 | IIB |
| T3 | N2 | M0 | III |
| T4 | Any N | M0 | III |
| Any T | Any N | M1 | IV |