Personalized dosing of FOLFIRINOX in Pancreatic Cancer patients: a phase-2 pharmacokinetic, safety and feasibility study

PERFUPANC

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PERSONALIZED DOSING OF FOLFIRINOX IN PANCREATIC CANCER PATIENTS: A PHASE-2 PHARMACOKINETIC, SAFETY AND FEASIBILITY STUDY

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CONFIDENTIALITY STATEMENT

This document contains confidential information that must not be disclosed to anyone other than the sponsor, the investigative team, regulatory authorities, and members of the Research Ethics Committee.

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ABBREVIATIONS

5-FU	5-fluorouracil
ABR	General Assessment and Registration form (ABR form), the application form that is required for submission to the accredited Ethics Committee; in Dutch: Algemeen Beoordelings- en Registratieformulier (ABR-formulier)
AE	Adverse Event
AR	Adverse Reaction
ALT	Alanine transaminase
AST	Aspartate transaminase
AUC	Area Under the Curve
BSA	Body Surface Area
CA	Competent Authority
CCMO	Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek
Css	Concentration at Steady State
CV	Curriculum Vitae
DFS	Disease Free Survival
DNA	Deoxyribonucleic Acid
DPD	Dihydropyrimidine dehydrogenase
DPYD	Enzyme encoded by dihydropyrimidine dehydrogenase
DSMB	Data Safety Monitoring Board
EU	European Union
EudraCT	European drug regulatory affairs Clinical Trials
FOLFIRI	FOLinic acid, Fluorouracil and IRInotecan
FOLFIRINOX	FOLinic acid, Fluorouracil, IRINotecan and OXaliplatin
FOLFOX	FOLinic acid, Fluorouracil and OXaliplatin
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)
HPLC	High-performance liquid chromatography
IB	Investigator's Brochure
IC	Informed Consent
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier

IRI	Irinotecan
LC-MS/MS	Liquid chromatography – tandem mass spectrometry
METC	Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)
MIPD	Model-Informed Precision Dosing
mFOLFIRINOX	Modified-FOLFIRINOX
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NONMEM	Nonlinear Mixed Effect Modelling
ORR	Overall Response Rate
OS	Overall Survival
OXA	Oxaliplatin
PBMC	Peripheral Blood Mononuclear Cells
PD	Pharmacodynamics
PFS	Progression Free Survival
PK	Pharmacokinetics
(S)AE	(Serious) Adverse Event
SN-38	Metabolite of irinotecan
SPC	Summary of Product Characteristics; in Dutch: officiële productinformatie IB1-tekst
Sponsor	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.
SPSS	Statistical Package for the Social Sciences
SUSAR	Suspected Unexpected Serious Adverse Reaction
TDM	Therapeutic Drug Monitoring
UAVG	Dutch Act on Implementation of the General Data Protection Regulation; in Dutch: Uitvoeringswet AVG
UGT	Uridine diphosphate glucuronyl transferase
WMO	Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen

1. SYNOPSIS

Rationale

The guideline for the treatment of pancreatic cancer recommends chemotherapy with the so-called FOLFIRINOX regimen. This is a triplet combination consisting of three anticancer drugs: 5-fluorouracil (5-FU), irinotecan and oxaliplatin. FOLFIRINOX is the most effective regimen compared with other treatment regimens and is therefore 1st-line treatment. However, the downside is that FOLFIRINOX is associated with a high incidence (76%) of serious adverse events. In addition, with regular dosing of these anticancer drugs, a large difference between patients is seen in systemic exposure. This exposure largely explains the extent of side effects, but is also predictive of the effect of these drugs. The therapeutic window for 5-FU is extremely narrow and its dosage remains largely empirical as it is based on body surface area (BSA). Previous study data show that with standard dosing, up to 75% of patients treated with BSA-dosed 5-FU achieve either too high or too low exposure of 5-FU. As a result, there is an increased risk of toxicity or reduced treatment efficacy. Here lies a great opportunity for improvement, as further adjustments in dose calculation according to individual parameters beyond BSA seem warranted. The PERFUPANC study will investigate whether treatment with FOLFIRINOX can be improved by uniquely adjusting the dose of 5-FU for each individual patient. We will do this based on individual patient characteristics and measured drug concentrations in blood with a population pharmacokinetic model, and is also known as model-informed precision dosing (MIPD). The main hypothesis of this study is that 5-FU MIPD will increase the likelihood of both effective and safe 5-FU treatment, which also improves quality of life. This will first be investigated in the current prospective multicentre phase-2 trial, to evaluate the safety and feasibility of our strategy for 5-FU. Additionally, the exposure-toxicity/exposure-response relationship of irinotecan will be explored to determine the safety and added value of irinotecan MIPD.

Objective

The PERFUPANC phase-2 trial is divided into two parts. The main objectives of PART A are:

- To validate the population $AUC_{0\text{-}46h}$ range of intravenous 5-FU in patients with pancreatic cancer treated with BSA based dosed FOLFIRINOX, and;
- To determine the percentage of patients treated with BSA based dosed FOLFIRINOX that achieves therapeutic (AUC) range of 5-FU, defined as an $AUC_{0\text{-}46h}$ target of 5-FU between 20 and 30 mg*h/L.

The main objective of PART B is:

- To determine the safety, model performance and feasibility of MIPD of 5-FU in pancreatic cancer patients treated with FOLFIRINOX.

Secondary objectives in both parts that are of particular importance, are:

- To develop a population 5-FU PK model for applying 5-FU MIPD in for patients treated with FOLFIRINOX.
- To identify patient and treatment characteristics that are correlated with 5-FU exposure/PK (variability) and 5-FU induced toxicity.
- To get insights in whether limited sampling of 5-FU samples is sufficient to safely adjust 5-FU dosing in routine clinical practice, and which limited sampling strategy is adequate for use.
- To get insights in the preliminary clinical benefit (ORR, OS, PFS) of MIPD of 5-FU, accounted for stage of disease.

- To establish the population irinotecan, SN-38 and SN-38G AUC range of intravenous irinotecan in patients with pancreatic cancer treated with FOLFIRINOX.
- To get insights in the safety and pharmacokinetics of irinotecan dosages in different UGT1A1 genotypes.

Main trial endpoint

PART A

- Percentage of patients undergoing FOLFIRINOX treated with standard (BSA)-dosed 5-FU achieving a 5-FU target AUC range (5-FU $AUC_{0\text{-}46h}$ between 20 and 30 mg*h/L) within two dose cycles of 5-FU. *This endpoint is assessed at treatment cycles 1, 2, and in subsequent FOLFIRINOX cycles in which 5-FU dose adjustments are applied (≥15%).*

PART B

- Percentage of patients undergoing FOLFIRINOX treated with 5-FU MIPD achieving a 5-FU target AUC range (5-FU $AUC_{0\text{-}46h}$ between 20 and 30 mg*h/L) within two dose cycles of 5-FU. *This endpoint is assessed at treatment cycles 1, 2, and in subsequent FOLFIRINOX cycles in which 5-FU dose adjustments are applied (≥15%).*

Secondary trial endpoints

- $AUC_{0\text{-}46h}$ of 5-FU and its metabolite in patients treated with FOLFIRINOX
- Incidence of grade ≥ 1-5 toxicity, hospitalization, treatment delay (> 2 days) and early treatment withdrawal in patients treated with FOLFIRINOX.
- Disease free survival, progression free survival, objective response rate and overall survival of patients treated with FOLFIRINOX
- Turn-around-time of 5-FU MIPD (or incidence of treatment delay due to 5-FU MIPD)
- Pharmacokinetics of 5-FU
- Pharmacokinetics of irinotecan and its metabolite SN-38 and SN-38G in UGT1A1 PMs, IMs and EMs
- Correlation of patient and treatment characteristics with AUC of 5-FU and/or irinotecan

Trial design

Multicentre, non-randomized phase-2 study to validate (**PART A**) the 5-FU $AUC_{0\text{-}46h}$ target range of the FOLFIRINOX-regimen, and to evaluate (**PART B**) the safety and feasibility of 5-FU MIPD strategy in pancreatic cancer patients undergoing FOLFIRNIOX treatment.

Trial population

Patients ≥ 18 years diagnosed with pancreatic cancer that will undergo FOLFIRINOX (classic or modified) chemotherapy at CZE, Amsterdam UMC, LUMC, Isala, or EMC. Main exclusion criteria are WHO performance status > 2, the inability to undergo extra blood sampling, substance abuse, psychotic disorders, and participation in conflicting studies (e.g. PREOPANC). A total of 100 patients will be included: 50 patients in PART A and 50 patients in PART B.

Interventions

PART A: Additional blood samples to establish 5-FU, irinotecan/SN-38 and oxaliplatin exposure will be drawn at a total of six time points (5 on day 1 of the treatment cycle, and 1 on day 3 of the treatment cycle) at cycle 1. In cycle 2, only three blood samples will be drawn (2 on day 1, and 1 on day 3). All

other procedures will be part of standard care. In subsequent cycles where 5-FU dose has been adjusted (≥15%) three blood samples will be drawn (2 on day 1, and 1 on day 3). All other procedures will be part of standard care

PART B: Additional blood samples as described at PART A will be drawn. Furthermore, MIPD of 5-FU will be implemented in all participating study sites. 5-FU will be dosed based on AUC (with 5-FU Pop-PK/MIPD model) and tolerability for each individual patient. All other procedures will be part of standard care.

Additional (PART A and PART B): For endogenous biomarker (ratio) concentrations of uracil/dihydrouracil (U/DHU) and thymine/dihydrothymine (T/DHU) (to assess DPD phenotype) a 4 mL blood sample will be taken at baseline. Intestinal microbiome data can be collected from patients included in this study by collecting one stool sample around cycle 1 of FOLFIRINOX treatment. ctDNA can be collected by taking one additional 10 mL blood sample at baseline and at each routinely performed CT-scan follow-up moment during FOLFIRINOX treatment.

Ethical considerations relating to the clinical trial including the expected benefit to the individual subject or group of patients represented by the trial subjects as well as the nature and extent of burden and risks

The risk associated with participation in this clinical trial is low. For PART A, the difference between the standard care (treatment with FOLFIRINOX) and this study is the additional blood sampling.

For PART B, the difference between standard care and the current study is as follows: additional blood sampling and 5-FU dosing based on AUC (intervention) and based on tolerance (standard care). 5-FU dosage may be increase, guided by the 5-FU MIPD model, to achieve 5-FU target AUC range. Patients may experience 5-FU side-effects upon dose increase. Therefore dose escalations will only be performed in patients with a good clinical and laboratory tolerance to FOLFIRINOX treatment, and a maximum dose increase of 20% in 5-FU dose intensity per cycle, and a maximum total 5-FU dose intensity of 130% (compared to BSA-dosed 5-FU) is applied in this study. On the other hand, 5-FU dose decrease based on AUC may lead to less 5-FU toxicity in patients with high 5-FU exposure (AUC).

The study burden for uracil/DHU/DHU/T, 5-FU, Irinotecan/SN-38 and Oxaliplatin TDM in cycle 1 is the 7x times blood sampling in all patients (total of 40 ml). For cycle 1, a venflon will be introduced in the peripheral vein of the patients to reduce the burden of multiple blood sampling. In cycle 2 and potential subsequent cycles, the study burden is 3x times blood sampling in all patients (total of 24 ml). The number of blood samples was designed to collect the minimum amount of blood that is required to accurately and completely calculate the $AUC_{0\text{-}46h}$ of 5-FU. If a patient agrees to additional sampling for ctDNA, the additional study burden of this is 10 ml blood sampling at baseline and every routine CT-scan moment during FOLFIRINOX-treatment. There is no significant risk associated with this venapuncture besides a small risk of thrombophlebitis and hematoma, which is similar to the risk of other venapunctures performed during routine treatment of the patient.

If a patient agrees to collect a stool sample, this poses only the minimal burden of extra time having to collect their own sample at home.

The benefit for the patient participating in this study is that the 5-FU dosing will be personalized to potentially reduce toxicity and/or maintain or improve efficacy of FOLFIRINOX treatment. If this strategy proves successful, personalized 5-FU dosing (by MIPD) will be applied in our standard routine care. In the future this will benefit all pancreatic cancer patients that are treated with FOLFIRINOX.

2. INTRODUCTION AND RATIONALE

2.1 Therapeutic condition and current treatment status

Pancreatic cancer and the FOLFIRINOX regimen

Pancreatic cancer (PC) is the fourth leading cause of cancer-related death, with only 24% survival at 1 year and 6% survival at 5 years after diagnosis. About 2900 new PC patients are diagnosed annually in the Netherlands, with about 50% of patients having metastatic PC at the time of diagnosis. Systemic chemotherapy is the cornerstone of the treatment of PC, for which FOLFIRINOX is the first-line treatment. FOLFIRINOX is a triplet treatment consisting of intravenous 5-fluorouracil (5-FU), irinotecan and oxaliplatin. Standard dosing of 5-FU in these intravenous chemotherapeutic regimens is based on body surface area (BSA) and consist of 400 mg/m^2 bolus in 15 minutes followed by 2400 mg/m^2 as a continuous infusion over 46 hours (table 1) (1-4).

In pancreatic cancer patients with metastatic disease, the superiority of FOLFIRINOX over gemcitabine monotherapy was established in the phase-3 ACCORD 11 trial, in which the objective response rate was significantly higher with FOLFIRINOX as compared to gemcitabine (32% versus 9% percent), as was median PFS (6.4 versus 3.3 months) and overall survival (11.1 versus 6.8 months) (5). Currently, a modified FOLFIRINOX (mFOLFIRINOX) regimen is also widely used in which the doses of irinotecan and fluorouracil are slightly reduced (table 2). mFOLFIRINOX showed similar outcomes to classic FOLFIRNOX (response rate 38%, median OS 11.2 months) in a phase-II study, but with a more favorable toxicity profile (6). In patients with resectable pancreatic cancer, the benefit of mFOLFIRINOX was shown in the PRODIGE-24 trial. In this trial, compared to gemcitabine alone, mFOLFIRINOX improved disease-free survival (DFS; median 21 versus 13 months, five-year DFS 26% versus 19%) and overall survival (OS) (median 54 versus 36 months, five-year OS 43% versus 31%) (7).

Table 1. The treatment protocol of classic FOLFIRINOX

Medication	Day 1	Day 2	Day 3	Day 4 – 14	Administration route (hours)	Dosage (mg/m2)
Irinotecan	x			Rest	iv (1h30min)	180
Oxaliplatin	x				iv (2h)	85
Leucovorin	x				iv (15min)	400
Fluorouracil	x				iv (5 min)	400
Fluorouracil	x	x	x		iv (46h)	2400

Table 2. The treatment protocol of modified-FOLFIRINOX (mFOLFIRINOX)

Medication	Day 1	Day 2	Day 3	Day 4 – 14	Administration route (hours)	Dosage (mg/m2)
Irinotecan	x			Rest	iv (1h30min)	150
Oxaliplatin	x				iv (2h)	85
Leucovorin	x				iv (15min)	400
Fluorouracil	x	x	x		iv (46h)	2400

Although FOLFIRINOX is currently the most effective treatment regimen for PC, up to 76% of patients experience severe toxicity and there are large variations in response rates between patients. This may be partly explained by inter-individual variability in the systemic exposure of both 5-FU and irinotecan when they are dosed on body surface area (BSA), potentially leading to under- and overexposure.
The first steps towards more personalized dosing to account for the inter-individual variability have already been taken with genotype-guided dosing of 5-FU and irinotecan: At least two metabolic enzymes, DPD for 5-FU and UGT1A1 for irinotecan, play key roles in the clearance of these drugs. Deficiencies in these enzymes, caused by e.g. corresponding gene variants, are associated with severe toxicity due to chemotherapy. Because genotyping variants of *DPYD* for 5-FU and *UGT1A1* for irinotecan has recently become best practice in the Netherlands, severe toxicity can be reduced by lowering the starting dose in patients with reduced DPD enzyme activity (~4% of patients) and UGT1A1 enzyme activity (~10-17% of patients) (8-11). Despite this, in current practice, inter-individual systemic drug exposure still varies significantly between patients, as *DPYD* and *UGT1A1* only partially explain chemotherapy-induced toxicity and because of the gene-enzyme activity variability in *DPYD* variant allele carriers.
For instance, *DPYD* variant alleles (*2A, *13, c.1236G>A, and c.2846A>T) have been established as predictors of 5-FU associated toxicity and carriers are now treated with a genotype-guided dose of 5-FU. However, there is a large variability between the *DPYD* genotype and DPD phenotype, especially for those with a gene activity score of 1.5. Some *DPYD* variant allele carriers can even tolerate up to standard doses of 5-FU without major toxicity (9,12,13). For UGT1A1, intermediate and normal metabolizers receive one and the same standard irinotecan dose, although normal metabolizers can tolerate higher doses. However, up titration of chemotherapeutic dosing is not often done in clinical practice when patients have no to little toxicity, even though this may come with a risk of underdosing (14-17).
Finally, the majority of the patient population does not carry a *DPYD* or *UGT1A1* variant allele, yet a significant proportion does experience (severe) toxicity from 5-FU and irinotecan. Toxicity outcomes in these patients remain largely unpredictable, and may be linked to the large inter-individual variability in 5-FU and/or irinotecan exposure. They too would therefore benefit from a more personalized dosing approach.

Thus, given the fact that both 5-FU and irinotecan remain the cornerstone in chemotherapeutic treatment of pancreatic cancer, further improvements to achieve personalized dosing of chemotherapeutics 5-FU and irinotecan are needed for better treatment outcomes.

2.2 Clinical trial rationale

BSA versus AUC based dosing of 5-FU – previous studies
It is well-known that 5-FU dosing based on body surface area (BSA) is correlated with wide variations in systemic 5-FU exposure, also known as Area Under the Curve (AUC) (18,19). The working group of the International Association of Therapeutic Drug Monitoring and Clinical Toxicology (IATDMCT) summarized previous clinical trial studies of 5-FU and observed approximately 40% interindividual variability in 5-FU exposure between all these studies. This is explained by many important factors that are not included in the standard BSA based dosing calculation formula such as individual 5-FU elimination rate, age, gender, body composition, disease state and organ function. Almost all clinical trials showed a relationship between 5-FU systemic exposure and 5-FU toxicity (20). Patients that suffered from fluoropyrimidine-induced toxicity had higher 5-FU plasma concentration than patients

without toxicity. Moreover, several studies showed association between low 5-FU exposure and reduced efficacy (21,22). Early studies by Gamelin et al. showed that patients who had AUC of 5-FU under 20 mg*h/L had less efficacy of the treatment than patients above this target (23), and observed increased toxicity above 24 mg*h/L in patients (19). Therefore, the 5-FU AUC target was initially 20-24 mg*h/L but this was based on 8-hour continuous infusion of 5-FU 1500 mg/m².

The IATDMCT showed in an extensive review by Beumer et al., that only 25% of the patients are within the therapeutic window and strikingly, 60% of the patients are underdosed after the first cycle (Figure 1). Similar results have recently been demonstrated by a prospective multicenter study in 434 gastrointestinal cancer patients treated with 5-FU, where the majority of patients (60.6%) were found to be underdosed and 19.1% of patients to be overdosed (24). This provides a great opportunity for treatment optimization to increase both efficacy as well as safety of treatment with 5-FU. Both over- and underexposure following 5-FU administration can be improved by Therapeutic Drug Monitoring (TDM). Using TDM instead of BSA based dosing is able to reduce the inter-individual variability in exposure and toxicity while improving or at least preserving efficacy.

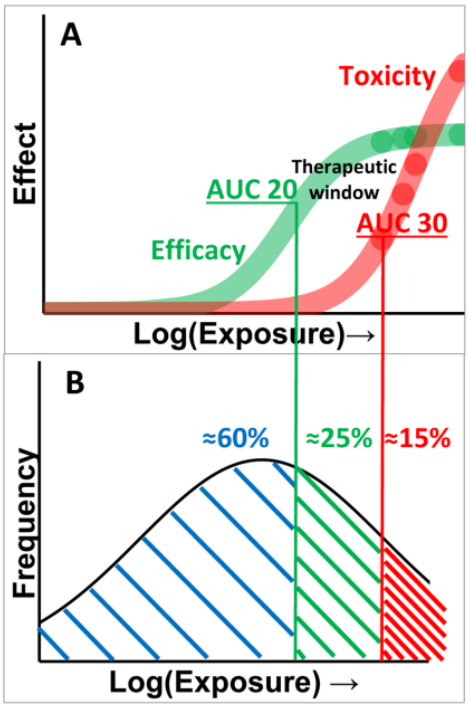


Figure 1. Schematic depiction of (A) the exposure-response (green, AUC≈20 mg·h/L) and exposure-toxicity (red, AUC≈30 mg·h/L) relationships of 5-FU, defining the therapeutic window of 20–30 mg·h/L. The commonly practiced BSA-based dosing results in (B) a population distribution of exposure (solid line) and associated cumulative frequency distribution (dotted line) that shows that ≈60% of patients are under-dosed, ≈15% of patients are over-dosed, and only ≈25% of patients will experience exposure within the therapeutic window.

One phase III RCT by Gamelin et al. compared BSA dosing with TDM of 5-FU in 208 patients with metastatic colorectal cancer. In the TDM arm, the 5-FU dose was adjusted when patients were not within the target window. The 5-FU dose was decreased in patients that had an AUC above the target window regardless whether patients experienced toxicity. The Objective Response Rate (ORR) was 33.7% in PK arm and 18.3% in BSA arm (P = 0.004). The median Overall Survival (OS) was 22 months in PK and arm 16 months in BSA arm (P = 0.08). Furthermore, the toxicity was significantly reduced in PK arm versus BSA arm (P = 0.03). Capitain et al. has also shown an improvement of efficacy in PK versus BSA arm in 118 patients with metastatic colorectal cancer. The ORR after 3 months was 69.7% in PK arm whereas 46.6% in BSA arm. The median OS and PFS were 28 and 16 months in PK arm respectively. In BSA arm the median OS and PFS were 22 and 10 months respectively. The toxicity (diarrhea and mucositis) was reduced in PK arm compared with BSA arm (25).

The initial target range (20-24 mg*h/L) has only an ≈20% range, which is rather small, especially given the significant intra-patient variability. Based on subsequent observational clinical studies and a review of the PK-PD data, the AUC target range was set to 20-30 mg*h/L, and applied to modern 46-hour continuous infusion schedules of 5-FU, as is now typically used with modern chemotherapy regimens, such as FOLFOX, FOLFIRI and FOLFIRINOX (26).
Currently, two TDM dosing algorithms were published in the literature. The algorithm by Gamelin is based on an old 5-FU regimen and is therefore not applicable in modern chemotherapy regimens. The algorithm by Kaldate was derived from retrospective analysis of a longitudinal dataset with AUC of 5-FU measurements from at least two consecutive cycles in colorectal cancer patients receiving FOLFOX6 regimen (26). The authors performed linear regression analysis of change in AUC of 5-FU versus change in dose for 307 cycle pairs in which a dose change was implemented. The Kaldate dosing algorithm with an AUC target of 20-30 mg*h/L is already validated in single-cohort clinical trial of Wilhelm et al (27). They showed that the TDM dosing algorithm with a maximum dose increase of 30% was effective in increasing the proportion of FOLFOX6 and FUFOX patients with 5-FU plasma exposure over time as well as lower incidence in severe 5-FU toxicity.

Almost all 5-FU TDM studies reduced significantly toxicity in patients treated with modern 5- FU regimen such as FOLFOX6, FOLFIRI and FOLFIRINOX. (18,21,27–31). Moreover, some of these TDM studies showed improvement in efficacy (30,31). Therefore, IATDMCT, strongly recommend TDM for the management of 5-FU therapy.

For PC patients treated with FOLFIRINOX, two studies have been published regarding the effect of 5-FU TDM in this population:

- Morawksa et al. (2018) used the Gamelin dosing algorithm to achieve a target 5 FU AUC of 18–28 mg*h/L within 3 cycles of chemotherapy in 28 patients. Results were pooled with other tumor types and 5-FU regimens. 50.7% of patients required dose adjustments after cycle 1. Percentage of patients within 5-FU AUC target range were 49.3%, 66.9%, 61.0% at cycle 1, 2 and 3, respectively ($p = 0.002$ cycle 1 vs cycle 2). At all 3 cycles, lower incidences of grade I/II toxicities were observed for patients below or within range compared with those above range (19.4% vs 41.3%, $p < 0.001$ respectively). These results confirmed 5-FU TDM can improve tolerability of 5-FU based chemotherapy in patients with gastrointestinal cancers (28).
- A recent study by Vilalta (2023) in 46 PC patients treated with mFOLFIRINOX found a significantly longer PFS for patients with a 5-FU AUC above 28 mg*h/L. Dosage was adjusted according to PK parameters using the Kaldate algorithm. The risk of progression was significantly reduced in patients with 5-FU AUC 28 mg*h/mL [HR = 0.251, 95% CI 0.096-0.656; $p = 0.005$] and CPT-11 AUC < 10 mg*h/L [HR = 0.189, 95% CI 0.073-0.486, $p = 0.001$]. This higher AUC target compared to that described in CRC patients might be justified by the pancreatic cancer stroma, which hinders the access of chemotherapy drugs to cancer cells. Therefore, higher drug concentrations might be required to exert an antitumoral effect. Considering tolerability, TDM-based dosing of mFOLFIRINOX treatment was associated with grade 3-4 toxicity in 61% of cases (32).

Model-informed precision dosing of 5-FU

Contributors to inter-individual variations of 5-FU include differences in chemotherapeutic regimens, for example, whether 5-FU bolus dosing was used, and patient characteristics (e.g. age, gender, disease status, organ functions, drug-drug interactions, DPD activity, and potentially body composition) (26). Combining blood sampling data and patient characteristics with mathematical approaches would

enable more appropriate dosing modifications for each patient. The available algorithms described in literature do not take patient characteristics into account for predicting AUC.
Because individual factors, other than dose change, also affect the change in AUC, in the current study, we will perform longitudinal PK monitoring to identify the most important contributors and develop a guiding population PK model. Therefore, in this study we will not only apply TDM, but will go one step further by applying model-informed precision dosing (MIPD), the evolved version of TDM. Shortly explained, MIPD involves the application of mathematical algorithms using simultaneous integration of patient covariates (i.e. a priori prediction), and individual drug concentration measurements (i.e. posteriori prediction). This allows to fully individualize drug dosing, and increase effectiveness of treatment. MIPD also enables predicting the ideal starting 5-FU dose for each individual, instead of determining 5-FU starting dose in cycle 1 on the basis of an empirical index, namely the BSA.

Intra-individual variability in 5-FU pharmacokinetics

The intra-individual variability of 5-FU exposure is approximately 20% (20). Previous clinical studies on 5-FU did not provide specific information on blood sample handling and accuracy of the 5-FU analysis. It is well-known that both 5-FU and the endogenous biomarker for DPD enzyme activity, uracil, are rapidly degraded by the DPD enzyme in peripheral blood mononuclear cells (PBMCs) in the blood sample. Therefore, we add a DPD inhibitor gimeracil to the sampling tubes prior to blood sampling as a solution to inhibit rapid breakdown of 5-FU after sampling. Most previous clinical studies did not add a DPD inhibitor to the 5-FU blood sample. This may have caused variability of 5-FU plasma concentration measurements and also to the dosing recommendations. To further decrease intra-individual variability we will sample two times within one cycle of continuous 5-FU infusion whenever possible.
Circadian rhythm may also contribute in the intra-individual variability in 5-FU plasma concentration. Fleming et al. observed higher plasma concentration of 5-FU at 6 am and lower plasma concentration at 3 pm during continuous infusion of 5-FU (33). Therefore, to reduce intra-individual variability by circadian rhythm chemotherapy the blood sampling will take place at the same time of the day each cycle for that individual patient. It is not feasible to start the chemotherapy at the same time of the day in every patient participating in this study. Therefore, we will retrospectively determine whether blood sampling time may contribute to inter-individual variation in 5-FU exposure AUC calculation.

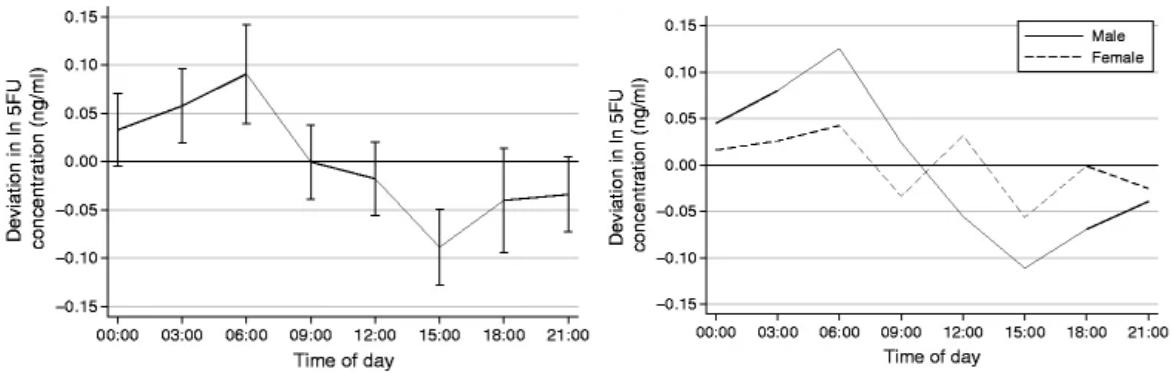


Figure 2. a. (left) Circadian variation in 5-FU concentrations during a 24-hour constant rate infusion and b. Sex difference in circadian rhythm (34).

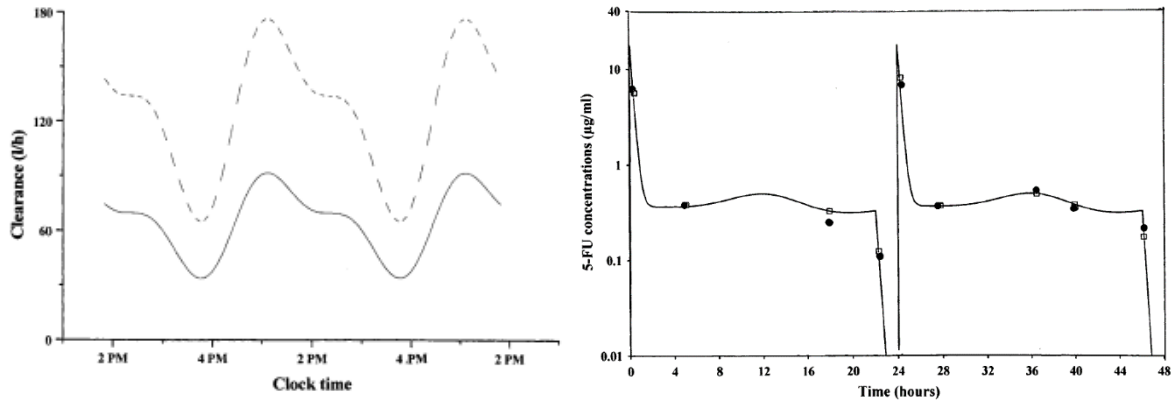


Figure 3.a. (left) Circadian variations in mean plasma concentration of 5-fluorouracil. Males (----); females (—) and b. (right) Typical posterior individual fittings of 5-FU concentrations over time after a loading dose (400 mg/m^2) followed by a continuous infusion over 22 hours (600 mg/m^2). ● Observed values, □ predicted values, 5-FU (34).

Another important issue concerns the AUC calculation. All previous TDM studies calculated AUC of 5-FU with a simple formula (Css x t), which is based on the average plasma concentration at steady state (Css) and the duration (t) of 5-FU continuous infusion. This formula does not include the exposure of 5-FU bolus and ignores its contribution to the 5-FU exposure. According to recent publication by Deyme et al., 5-FU bolus might contribute to the total AUC of 5-FU with estimations ranging from 20 to 50% (35). In current clinical practice, oncologists often remove 5-FU bolus in the next cycle to reduce toxicity, unaware of the contribution it had to the total 5-FU exposure. In PC, the mFOLFIRINOX regimen does not include a 5-FU bolus. Therefore in this study we will determine the contribution of 5-FU bolus injection by comparing the AUC of 5-FU calculated with our new population PK model with the AUC calculated with the simple formula (Css x t), and by comparing calculated AUCs of classic and modified FOLFIRINOX regimens. Additional factors that have not been taken into account by the simple Css x t formula calculated with only one Css sample, are circadian rhythm of 5-FU, variations in infusion rate (given the short half-life of 5-FU), and variability time to Css. For this reason, in the current study we will calculate AUC based on multiple samples and from there on investigate a limited sampling strategy.

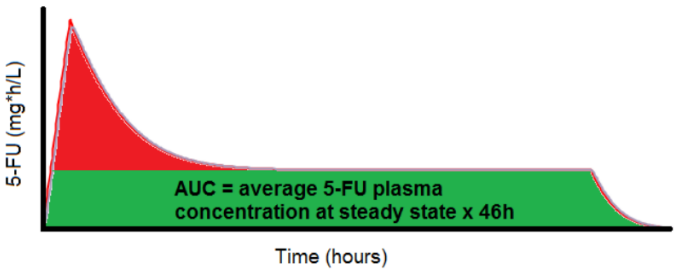


Figure 4. Artist impression of the AUC of a modern 5-FU dosing schedule which consist of 400 mg/m^2 bolus infusion in 4 minutes and 2400 mg/m^2 as a continuous infusion over 46 hours. The latter results in 5-FU steady state. All previous TDM studies calculated the AUC of 5-FU (shown in red) with simple formula which is based on average 5-FU plasma concentration at steady state and duration of 5-FU continuous infusion (46h) ignoring the contribution of 5-FU bolus (shown in green).

Rationale 5-FU TDM in PERFUPANC

In our study, we want to increase the percentage of patients within the target range and we ultimately aim to achieve optimal dosing of 5-FU immediately from the first cycle onwards. Dose optimization within the dose target of 20 to 30 mg*h/L in order to aim for an AUC of 25 will be used as a reference range.

Importantly, 5-FU TDM dosing algorithms have demonstrated beneficial effects in other tumors, but the impact of 5-FU pharmacokinetics on efficacy and toxicity in PC patients treated with FOLFIRINOX is largely unknown. Therefore in PART A of this study, the population pharmacokinetics of 5-FU in our PC patient population with FOLFIRINOX will be characterized to; 1] identify factors that influence 5-FU PK and 2] to validate the target $AUC_{0\text{-}46h}$ range of 20-30 mg*h/L for 5-FU described in literature for the PC population. This will allow us to establish a 5-FU Pop-PK/MIPD model relevant for our population. This 5-FU Pop-PK/MIPD model will be developed using the dataset from PART A. Our goal is to combine this PK model with minimal 5-FU sampling to provide a better and robust 5-FU dosing advice to be tested in future trials. Individualizing 5-FU dosing through MIPD may thereby reduce toxicity of treatment while maintaining efficacy, or even improve efficacy (Figure 5). In this study we will use a FU Pop-PK/MIPD model to adjust 5-FU dosages, because that has been tested in other 5-FU TDM studies and proven to be safe (18,21,27–31). Furthermore, we will use the 5-FU Pop-PK/MIPD model to calculate the optimal initial dose for the individual patient. Lastly, while other studies had primary endpoints solely based on the AUC target values, we also take 'dose reduction due to toxicity' in account, because in oncology medical practice this is a major parameter for dose individualization.

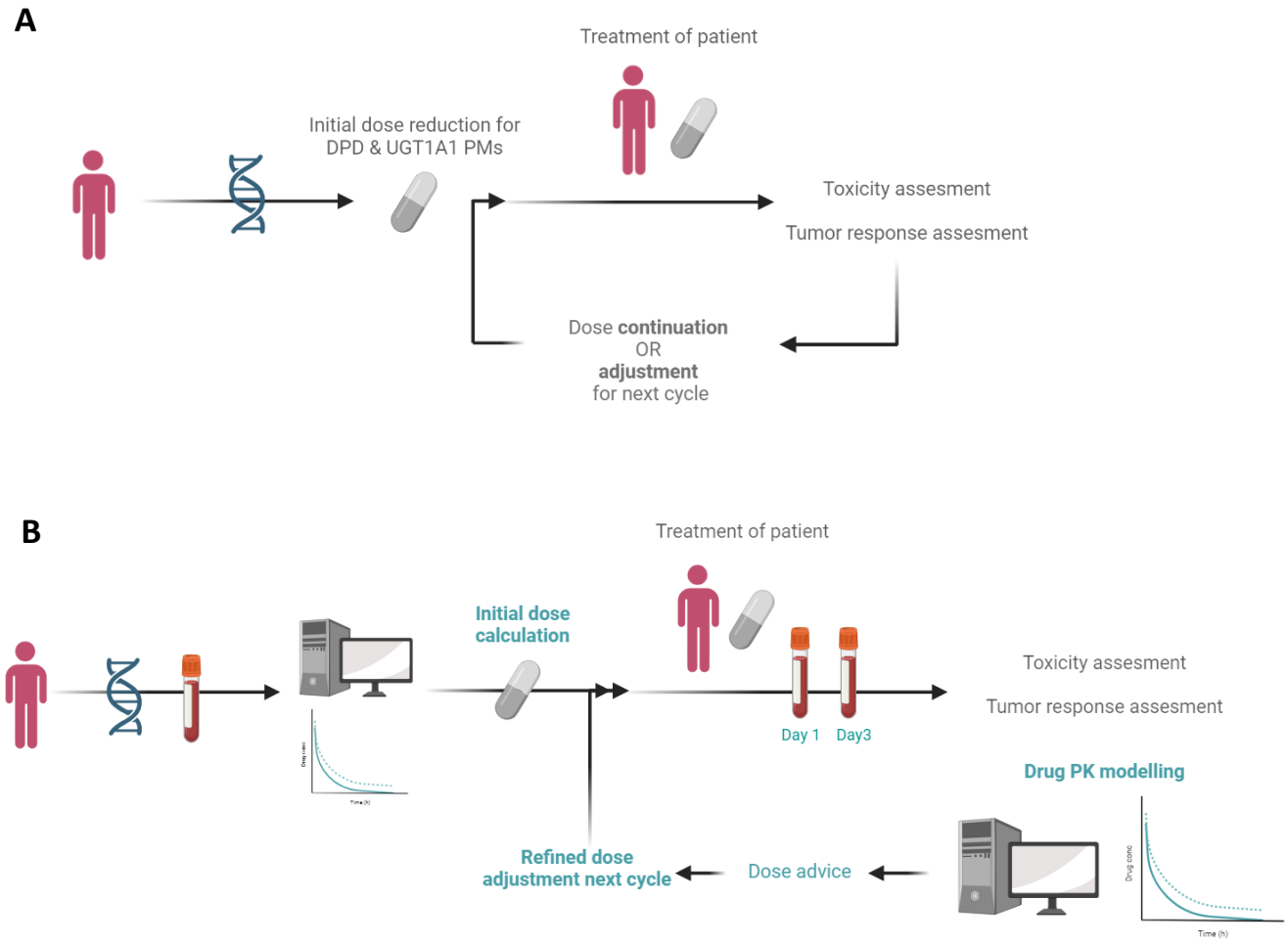


Figure 5. Schematic depiction of the FOLFIRINOX dosing strategy used in routine clinical practice (A) and the personalized FOLFIRINOX dosing strategy that proposed in the current PERFUPANC phase-2 study (B). In the personalized FOLFIRINOX dosing strategy, pharmacological interventions are added to the current standard-of-care in order to better individualize dosing for every patient. This new intervention consists of model informed precision dosing of 5-FU and is indicated in blue (B) .

***UGT1A1* genotype-guided dosing of irinotecan – opportunities for improvement**

Although UGT1A1 is the most well-known enzyme involved in the pharmacokinetics of irinotecan, many other enzymes play a role in its biotransformation. Irinotecan is a prodrug that is activated by carboxylesterase to SN-38. In addition, irinotecan undergoes CYP3A4/5-mediated oxidation into the inactive metabolites APC and NPC. Irinotecan uptake and transport into the hepatocytes is facilitated by membrane transporters such as SLCO1B1 and the ABC-transporter family. The main enzyme responsible for the inactivation of SN-38 is uridine diphosphate glucuronyl transferase (UGT)1A1, that glucuronidates SN-38 into SN-38- glucuronide (SN-38G). Also other UGT1A enzymes are involved in the inactivation of SN-38, such as UGT1A7 and UGT1A9, however to a lesser extent than UGT1A1.
In standard practice, in patients with reduced UGT1A1 activity, also known as poor metabolizers (PMs), the starting irinotecan dosing is reduced to 70% to reduce toxicity (36). However, in case of good tolerance doses are rarely increased. Furthermore, new studies are revealing that patients with a normal UGT1A1 enzyme activity, known as normal metabolizers (NMs), can tolerate higher than standard irinotecan doses, thereby increasing the likelihood of adequate clinical response without compromising safety. Therefore, a way by which dosing of irinotecan could be further personalized is by moving to full *UGT1A1* genotype-guided dosing of irinotecan.

The extensive review by Karas et al. (2022) summarized that UGT1A1 normal and intermediate metabolizers could tolerate irinotecan doses substantially higher than standard doses (14). For single-agent irinotecan (350 mg/m2 every 3 weeks), patients carrying *UGT1A1**1/*1 and *1/*28 could tolerate irinotecan up to 850 mg and 700 mg (corresponding to 500 mg/m2 and 412 mg/m2 assuming an average body surface area of 1.7 mg/m2), respectively, whereas those with *28/*28 could tolerate irinotecan up to 400 mg (235 mg/m2) (37). The plasma exposure to SN-38 was similar between these three genotype groups. For FOLFIRI (irinotecan dose, 180 mg/m2 every 2 weeks), patients with European ancestry carrying *UGT1A1**1/*1 and *1/*28 could tolerate irinotecan up to 370-390 mg/m2 and 310-340 mg/m2 , respectively, (38,39), whereas those with *28/*28 could tolerate irinotecan up to 130 mg/m2 (39). Similarly, patients with Asian ancestry carrying *UGT1A1**1/*1 and *1/*28 or *1/*6 could tolerate irinotecan up to 330 mg/m2 and 300 mg/m2 (40). For FOLFIRI plus bevacizumab, patients with European ancestry carrying *1/*1 and *1/*28 could tolerate irinotecan up to 310 mg/m2 and 260 mg/m2 , respectively (41). Currently, the maximum tolerated dose of irinotecan on the basis of the *UGT1A1* genotype has not been established yet for FOLFIRINOX (14).

So far, only a few studies have described dose-response/toxicity relationships between UGT1A1 activity subgroups. The systematic review by Miarons et al, described several studies that have analyzed the efficacy and safety of using high-dose irinotecan (> 180 mg/m2) in the FOLFIRI scheme for the treatment of mCRC , depending on the UGT1A1 genotype of the patients (16). The published results indicate that doses higher than 180 mg/m2 are tolerated by patients who are non-poor metabolizers for the UGT1A1 gene, and that these patients not only tolerate higher doses, but also achieve better efficacy results with these doses, both in terms of ORR (15,42-44) and PFS (17,42,45) and even, in some cases, in OS (42,45). Only one of the studies included in this review showed no differences with the use of higher doses of irinotecan in patients without UGT1A1 mutation (46).

These results imply dose-escalations of irinotecan may be necessary for increasing anti-cancer efficacy, especially in UGT1A1 normal metabolizers. However, other studies have found no difference in efficacy outcomes between UGT1A1 intermediate and normal metabolizers (47). To confirm the impact of UGT1A1 status and irinotecan dose escalations on the efficacy and safety profile of irinotecan, we consider that a comparative prospective study with a larger population is needed.

Irinotecan/SN-38 TDM

As is the case for 5-FU, irinotecan dosing based on body surface area (BSA) is correlated with wide variations in AUC, with a large interindividual variability in pharmacokinetic parameters of approximately 30% (48,49). Various population pharmacokinetic models have been described, the most recent being by Deyme et al., which looked at irinotecan and its four metabolites in 109 CRC patients treated with FOLFIRI or FOLFIRINOX regimen (50).

Aside from the impact of UGT1A1 functionality, the wide interindividual variability in irinotecan clearance is still not completely understood. Primarily, a decreased clearance in patients with altered hepatic function has been described (48,51,52). Additionally, increasing age may negatively influence irinotecan clearance, although this could not be confirmed in another analysis (48,53). Conflicting effects of gender on irinotecan pharmacokinetics have also been proposed. Several studies reported higher irinotecan exposure in women, which, in part, could be explained by decreased SN-38 (metabolic) clearance (48,52,54), while others found no gender effect (48,53,55). Several factors such as dose, timing of administration, enzyme activity, and hematocrit levels might be responsible for these differences. Worse clinical performance has been demonstrated to decrease irinotecan clearance (52). However, interindividual variability does not seem to be related to body size measures such as body surface area (BSA). Although irinotecan dose is generally based on BSA, it has been shown that BSA and other body size measures do not predict irinotecan pharmacokinetics (48,53,56).

Contrary to 5-FU, AUC target ranges for irinotecan and/or SN-38 have not been established yet in literature. Conflicting results have been reported regarding the relationship between irinotecan and SN-38 exposure and toxicity. An initial study suggested the biliary index (i.e. the ratio of SN-38 to SN-38G AUCs multiplied by the AUC of irinotecan) as a better predictor for gastrointestinal toxicity (57). Studies on this subject have been contradictory; a higher biliary index was significantly correlated with a higher incidence of severe diarrhea in several studies (48,55,57,58), whereas no significant association was found in other studies (48, 59-61).

Population pharmacokinetics and pharmacodynamics of irinotecan and active metabolite SN-38 from phase I trials showed that irinotecan and SN-38 AUC correlated significantly with irinotecan-induced toxicity (neutropenia, gastrointestinal toxicity), as well as with the intensity of the toxicities observed. A dose-effect relationship was also noted for anti-cancer activity since most tumor responses were observed at the highest doses administered, suggestive of an irinotecan/SN-33 exposure-response association (51). Furthermore, a multicompartmental pharmacokinetic model of irinotecan and its metabolites established a direct correlation between minor levels of irinotecan AUC and analytical covariables such as platelets, leukocytes and neutrophils count, suggesting a higher exposure to the active metabolite SN-38 (62).

So far, little is known about the relationship between irinotecan/SN-38 exposure and anti-cancer efficacy. The results from a recent study by Vilalta et al. in 46 PC patients suggested a longer progression-free survival in patients with irinotecan AUC < 10 mg*h/mL. In the study, the risk of progression was significantly reduced in patients with irinotecan AUC < 10 0 mg*h/L [HR = 0.189, 95% CI 0.073-0.486, p = 0.001]. The disposition of SN-38 has been shown to be dependent on the irinotecan provisions in previous pharmacokinetic studies. Thus, patients with irinotecan AUC ≥ 10 might present lower time to progression due to less conversion and, therefore, lower exposure to the active metabolite SN-38 (32).

Irinotecan administration based on circadian timing improved clinical outcome in several clinical trials (63-65), probably due to the circadian rhythm of enzymes and transporters involved in irinotecan

pharmacokinetics and pharmacodynamics (48,66). However, pharmacokinetic consequences have only been investigated in a small randomized study in which an increased metabolic ratio (SN-38/irinotecan AUC) and smaller interindividual variability were found after circadian-timed dosing (66). These results also point towards an exposure-response relationship.

Considering the large inter-individual variability in irinotecan and SN-38 exposure, new studies with prospective pharmacokinetic analysis of irinotecan and SN-38 are required to elucidate its role in terms of treatment efficacy and toxicity, as well as the impact of covariates on irinotecan/SN-38 pharmacokinetics. TDM of irinotecan and SN-38 may be of added value to reduce interpatient variability in exposure, as well as improve efficacy and reducing toxicity of irinotecan. TDM may also aid in guiding irinotecan dose escalations in normal or intermediate metabolizers, or even poor metabolizers with good tolerability. Therefore, in the PERFUPANC-study, TDM of irinotecan and the feasibility/safety of irinotecan dose escalations will be explored by determining irinotecan/SN-38 exposures in different UGT1A1 activity groups.

Additional analyses

As part of the current study, by collection of the following additional data/material we can answer study exploratory questions/objectives within the field of pancreatic cancer and FOLFIRINOX treatment:

<u>Oxaliplatin</u>

The added value of Oxaliplatin TDM (through assessing population AUC and variability) will be explored exploratively.

<u>Dried Blood Spot</u>

There have been new developments in the field of dried blood spot (DBS) measurements for 5-FU (86,87). For optimum 5-FU TDM, sample timing is crucial, along with the need for a venepuncture blood sample to obtain the plasma currently used for 5-FU measurement. In addition to complex blood sample handling requirements, large sample volume and frequent sampling required for pharmacokinetic analysis is another barrier to successfully implementing TDM in a healthcare setting. Microsampling in the form of dried blood spot (DBS) measurements, is an alternative collection method to venepuncture, which, combined with the now readily available liquid chromatography mass spectrometry (LC-MS/MS) technology, can overcome the plasma-associated issues. It also has the significant advantage of enabling at home and remote sampling, thus facilitating 5-FU TDM in clinical practice. We would like to add these DBS measurements to the study protocol for validation of 5-FU DBS measurements. We want to use DBS at the same sampling times as the plasma determinations. DBS is a finger prick which is a minimal burden for the patient. By adding DBS to the study for validation of 5-FU DBS, future patients can benefit if DBS can be used as a validated method to determine 5-FU in the future, because DBS is less burdensome.

<u>Patient reported outcome measures (PROMs)</u>

Through periodic (online) questionnaires, patients will be asked about their health status. This will be conducted using validated questionnaires in collaboration with two patient organizations active in the field of pancreatic tumors, SPKS and AVKV, as part of the standard-of-care Dutch Pancreatic Cancer Project (PACAP). PROMs will be used in sub-analyses to assess association with 5-FU, Irinotecan/SN-38 and Oxaliplatin plasma concentrations and for getting insights in the effect of MIPD of 5-FU on PROMs.

Body composition

Cachexia-associated adverse body compositions have a strong negative impact on survival, therapy-associated toxicity, and cancer treatment outcome (72-78). The individual body composition of patients with cancer may also affect the distribution of chemotherapeutic agents according to their hydrophilic or lipophilic properties. Using routine-care CT-scans for body composition analysis, it has been shown that low adipose tissue mass and high ectopic fat content in skeletal muscle (myosteatosis) are associated with shorter survival in patients with pancreatic or colorectal cancer (72,77,78). Recently, Mosamatic (www.mosamatic.com) was developed by MUMC, an artificial intelligence-based approach for automated analysis of CT-scans (79). A prototype deep learning neural network was trained using a multi-center collection of 3413 abdominal cancer surgery subjects to automatically segment skeletal muscle and subcutaneous as well as visceral adipose tissue at the L3 lumbar vertebral level. Segmentations were externally tested using challenging CT scans of 233 polytrauma subjects with suboptimal image quality (79), and further validated with a multi-center collection of >2500 CT-scans. The concordance between manual annotation of these CT scans and the algorithm was very high for skeletal muscle radiation attenuation (a parameter reflecting myosteatosis), the visceral adipose tissue volume, and subcutaneous adipose tissue volume (0.92-0.99), and the algorithm correctly identified sarcopenia in 90% of all cases without hands or arms in the field of view of the CT scan. It has also been shown that these body composition parameters are associated with chemotherapy-induced toxicity (*paper under review*). Therefore, as exploratory objective, we will investigate the association between body composition and the exposure of chemotherapeutic agents, skeletal muscle mass, visceral adipose tissue mass, subcutaneous adipose tissue mas, as well as the radiation attenuation of these tissue compartments will be analyzed for their correlation with circulating levels of 5-FU and its metabolites. Furthermore, the association between these body composition features and 5-FU-related toxicity will be investigated. Available routine diagnostic abdominal CT-scans will be analyzed by Mosamatic (MUMC). In this way, body composition features may be identified as covariates for 5-FU exposure and toxicity.

ctDNA

Liquid biopsy, particularly circulating tumor DNA (ctDNA) liquid biopsy, has shown promise as an adjunct to our standard care for pancreatic cancer patients. For instance, surveillance for recurrence or progression of PC currently involves traditional tumor markers such as CA19-9 and cross-sectional imaging. Further incorporating ctDNA guided surveillance may aid in the development of risk-adjusted treatment strategies for guiding chemotherapy. In the current study we can assess ctDNA dynamics over time (NGS or specific Pancreas ctDNA panel), to get insights in tumor response (sensitivity/resistance) to FOLFIRINOX treatment in pancreatic cancer patients, in order to explore the additional value of liquid biopsies as an early biomarker for treatment response. The short half-life of ctDNA in circulation is ideal for assessing response to therapy in shorter intervals (80).

Microbiome

The metabolism of irinotecan consists of multiple steps as described earlier. The inactive metabolite of irinotecan, SN-38G, is transported to the gut lumen by biliary excretion. Literature data suggest that SN-38G is reactivated to SN-38 in the gut by bacterial enzymes which produce bacterial metabolites called β-glucuronidases. This leads to the hypothesis that the presence of high amounts of β-glucuronidase-producing bacteria will lead to enhanced concentrations of intestinal SN-38, that in turn may contributes to increased risk of irinotecan-induced gastrointestinal toxicity such as severe diarrhoea.

Several preclinical studies have investigated modulation strategies to inhibit the intestinal bacterial metabolite β-glucuronidase and to improve the gut microbiome composition in order to reduce toxicity (88,89). However, limited evidence is available to confirm the correlation between a higher abundance and activity of β-glucuronidase and irinotecan-induced toxicity in human. We hypothesise that high activity of the gut microbiota-derived enzyme β-glucuronidase will be associated with increased gastrointestinal toxicity and decreased QoL and OS. Therefore, an exploratory aim of this study is to measure the intestinal concentrations and activity of β-glucuronidase and see whether there is a correlation with the frequency and severity of irinotecan-induced toxicity in human.

2.3 Concluding remarks/summary

Pharmacokinetic and pharmacodynamic data exist for 5-FU and irinotecan and both chemotherapy drugs have a narrow therapeutic window. For this reason, it is particularly relevant to achieve an optimal drug exposure within the therapeutic range based on pharmacokinetic parameters. In the present study, we will study dosage individualization of conventional chemotherapy by easily obtained pharmacokinetic parameters in daily practice to improve the toxicity profile while maintaining treatment efficacy and potentially improving tumor response in PC patients treated with FOLFIRINOX. 5-FU dose adjustment based on 5-FU AUC allows to increase the number of patients within the therapeutic range. Thereby, therapeutic drug monitoring of 5-FU may prevent both underdosing as well as toxicity in all 5-FU containing treatment regimens, including FOLFIRINOX in PC. The therapeutic range of 5-FU in the older regimens is defined by a target AUC of 20-30 mg*h/L. To the best of our knowledge the population exposure to 5-FU in FOLFIRINOX in PC and the percentage of PC patients treated with FOLFIRINOX reaching the therapeutic AUC has hardly been studied. 5-FU in the FOLFIRINOX regimen is given with or without a bolus in a high dose of 2400 mg/m^2 as a 46-hour infusion. This means that a comparable dose of 5-FU is given with FOLFIRINOX and other better-studied regimens like FOLFOX. As a result, exposure to 5-FU will be comparable between these different 5-FU regimens. Therefore, we hypothesise that the therapeutic range of 5-FU in FOLFIRINOX will be comparable to the target AUC of 20-30 mg*h/L in the older regimens and we expect that a significant part of patients will be outside this therapeutic window.
Despite sufficient evidence on the ability of TDM of 5-FU to reduce toxicity, while preserving the efficacy of 5-FU treatment, several problems such as wide intra-individual variation of 5- FU exposure, technical handling of blood samples, calculation of 5-FU exposure and 5-FU dosing advice need to be clarified before introducing TDM of 5-FU in standard routine clinical care. In this study, we hypothesize that TDM of 5-FU and the use of MIPD of 5-FU will increase the number of patients within therapeutic range and improve efficacy and safety. Therefore the aim of this study is to validate whether TDM of 5-FU is an effective tool to regulate individual 5-FU exposure in 5 Dutch Hospitals, while gathering data to further improve safety and minimize patient discomfort.

PART A of the PERFUPANC phase 2 study is crucial to validate the AUC target range of 5-FU established in earlier pharmacokinetic (PK) studies (figure 1, page 17). Since the proposed therapeutic $AUC_{0\text{-}46h}$ range (20-30 mg*h/L) of 5-FU is based on previous PK studies among various patient populations, it is first essential to validate the 5-FU AUC range for the PC patient population treated with FOLFIRINOX. The 5-FU AUC target range forms the foundation of the 5-FU MIPD model for guiding 5-FU precision dosing. After validation in our pancreatic cancer population, the validated therapeutic 5-FU $AUC_{0\text{-}46h}$ range of 20-30 mg*h/L will be used in PART B of this phase 2 study for MIPD (model built from PART A dataset). Simultaneously, the population pharmacokinetics of irinotecan and SN-38 will be assessed and the exposure-toxicity/exposure-response relationship of irinotecan/SN-38 will be explored to determine the added value of irinotecan dose escalations and TDM of irinotecan/SN-38.

PART B of the PERFUPANC phase 2 study serves to establish the feasibility, model performance and safety of 5-FU MIPD by implementation of MIPD of 5-FU in clinical practice. The 5-FU Pop-PK/MIPD model will prospectively be applied to dose 5-FU in PC patients receiving FOLFIRINOX until the 5-FU target AUC or dose-limiting toxicity is reached. The data collected in PART B will also be used for further refined pharmacokinetic analyses of 5-FU, irinotecan and oxaliplatin (population pharmacokinetics and target AUC range). We hypothesize that MIPD of 5-FU will further significantly reduce inter-individual variation in drug exposure and increase both the safety and efficacy of this treatment.

The current study is an important step towards precision oncology in dosing of classical anticancer drugs, and MIPD of 5-FU could potentially also be applied for patients treated with 5-FU in general. In this study the pharmacokinetics of FOLFIRINOX and the safety, model performance and feasibility of 5-FU MIPD will be determined. Demonstrating the feasibility and safety of our approach is essential before the initiation of a future planned randomized controlled phase III trial in which the added value (efficacy in PFS/OS, safety/tolerability and QoL) of 5-FU MIPD compared to the current standard practice of BSA-based 5-FU dosing in PC patients will be evaluated.

3. STRUCTURED RISK ANALYSIS

Treatment as proposed in this study uses the registered products 5-FU, leucovorin, oxaliplatin and irinotecan within a standard indication. For 5-FU, in PART B of the current study 5-FU doses may be increased or decreased to reach target AUC. Irinotecan, oxaliplatin and leucovorin are dosed as standard-of-care. Therefore, chapter 13.1 is only applicable for 5-FU. Chapter 13.2 provides the synthesis of the risk analysis.

3.1 Potential issues of concern

a. Level of knowledge about mechanism of action

5-FU is broken down into three active metabolites where they inhibit critical enzymes in the cell. One of these active metabolites, fluorouridine triphosphate (FUTP) is incorporated in the RNA whereas the other active metabolite, fluorodeoxyuridine triphosphate (FdUTP) is incorporated in the DNA. Both incorporations cause sufficient damage to the RNA and DNA which ultimately leads to cell death. Metabolite fluorodeoxyuridine monophosphate (FdUMP) interrupts thymidylate synthase (TS) activity by blocking the synthesis of pyrimidine thymidine. More detailed information about the mechanism of 5-FU can be found in the review by Longley et al (67).
See also SPC (summary of product characteristics).

b. Previous exposure of human beings

FOLFIRINOX (classic and modified) is a standard 5-FU combination therapy in and pancreatic cancer.
See also SPC of 5-FU.

c. Induction of the mechanism in animals and/or *ex-vivo*

5-FU is an old drug (developed in 1957) which has been tested in many in vitro, animal and ex-vivo human cell material before. It is already considered to be safe and therefore it is now widely used to treat variety of cancers.
See also SPC of 5-FU.

d. Selectivity of the mechanism

5-FU is an old drug (developed in 1957) which has been tested in many in vitro, animal and ex-vivo human cell material before. It is already considered to be safe and therefore it is now widely used to treat variety of cancers.
See also SPC of 5-FU.

e. Analysis of potential effect

See section 1.1 and t review by Beumer (20).
See also SPC of 5-FU.

f. Pharmacokinetic considerations

Detailed information on pharmacokinetics of 5-FU can be found in the review by Heggie et al (68).
See also SPC of 5-FU.

g. Predictability of effect

Several studies showed a relationship between 5-FU exposure and clinical effect. Patients with high 5-FU exposure had better response than patients with low exposure. Although the group who had high exposure had more risk developing severe toxicity.
See also SPC of 5-FU.

h. Interaction with other products

See Summary of Product Characteristics (SPC) of 5-FU in section 4.5, page 6.

i. Managing of effects

In case of 5-FU-induced toxicity, patients are treated with standard supportive care until the toxicity has been diminished.

j. Study population

Patients diagnosed with pancreatic cancer undergoing FOLFIRINOX.

3.2 Overall synthesis of the direct risks for the research subjects

Multiple blood sampling will be performed in both PART A and PART B, most of them during the first treatment cycle. This may damage peripheral veins. To reduce potential damage, a venflon will be introduced on day 1 of a treatment cycle in order to reduce the damage of the peripheral vein and also reduce the patient burden. Taking blood samples is a small risk for the patient but it can cause redness or swelling at the injection place. Some people can get lightheaded, faint or nauseous. Additionally, a limited sampling strategy will be evaluated after completion of PART A, and if feasible, will be used in PART B to reduce the amount of required blood samples.

<u>PART A</u>
The intervention of PART A consists only of multiple blood sampling of 5-FU, irinotecan and oxaliplatin. Patients will be treated according to the SPC and (inter)national clinical guidelines, therefore there is no extra risk when participating in this study compared to standard practice care.
In PART A, the AUC target range of 20-30 mg*h/L for 5-FU will be validated for pancreatic cancer patients undergoing FOLFIRINOX, to determine if this target range is feasible to use for AUC-guided dosing. A 5-FU Pop-PK model/MIPD algorithm for calculating dose escalations/reductions to reach a 5-FU $AUC_{0\text{-}46h}$ target range of 20-30 mg*h/L will be developed from the dataset collected in PART A, in order to account for relevant patient and treatment characteristics. After completion of PART A, an independent DSMB will evaluate whether PART B of the current study can be initiated.

<u>PART B</u>
Next to multiple blood sampling of 5-FU, irinotecan and oxaliplatin, 5-FU doses will be adjusted on an individual basis to reach 5-FU target AUC range. For irinotecan, oxaliplatin and leucovorin, patients will be treated according to the SPC, therefore there is no extra risk regarding these compounds.
In PART B, we want to adjust the 5-FU dosages in FOLFIRINOX chemotherapy to regulate individual 5-FU exposure in all participating hospitals. 5-FU dosages will be adjusted on an individual level based on the 5-FU Pop-PK/MIPD model (calculated dose to reach target AUC). With this intervention we want to increase the percentage of patients within the target AUC within two (!) dose cycles to achieve optimal dosing of 5-FU from the first treatment cycle onwards. Therapeutic Drug Monitoring of 5-FU

has been proven effective to reduce toxicity, while at least maintaining the efficacy of 5-FU treatment in oncology patients.

5-FU dose escalation may be required to regulate individual 5-FU exposure. In order to prevent overdosing and toxicity of 5-FU upon dose increase, multiple blood samples will be drawn in the first cycle to accurately determine the actual exposure of 5-FU and reliably calculate the dose advice of the second cycle. The accurate determination of the 5-FU exposure in the initial cycle, assures safe dose recommendations for the subsequent 5-FU cycles. Wilhelm et al. showed that Kaldate dosing algorithm with a maximum dose increase of 30% was effective to increase percentage of patients within the target range of 20-30 mg *h/L within four dose cycles (27). For this reason, the maximum 5-FU dose intensity in this study is set at 130% (meaning 30% increase in dose-intensity compared to the BSA-calculated dosing) as an extra safety measure. Dose-escalations per cycle are allowed to increase with a maximum of 20% in absolute dose-intensity per cycle. Lastly, while other studies had primary endpoints solely based on the AUC target values, we also take 'dose reduction due to toxicity' in account, because in oncology medical practice this is a major relevant parameter for dose individualization.

An additional safety measure is the fact that the calculated dose advice of the pharmacist, will judged by the oncologist, who decides whether the new 5-FU dose is suitable for the patient based on their current clinical status. Oncologists in the participating hospitals have extensive experience in recognizing and managing 5-FU toxicity, as this toxicity is often observed in standard clinical practice

The benefit risk ratio of 5-FU TDM is high since it reduces toxicity while maintaining the efficacy of the treatment.

4. OBJECTIVES AND ENDPOINTS

4.1 Primary and secondary objectives

Table 3. *Primary and secondary objectives with corresponding endpoints*

Objectives	**Endpoints**
Primary objectives	**Endpoint(s) for the primary objectives**
PART A • To validate the population AUC range ($AUC_{0\text{-}46h}$) of intravenous 5-FU in patients with pancreatic cancer treated with FOLFIRINOX. • To determine the percentage of patients treated with BSA-dosed FOLFIRINOX that achieves therapeutic (AUC) range of 5-FU, defined as an AUC target of 5-FU $AUC_{0\text{-}46h}$ between 20 and 30 mg*h/L.	**PART A** ***Primary endpoint*** • Percentage of patients undergoing FOLFIRINOX treated with standard-dosed (BSA) 5-FU achieving a 5-FU target AUC range (5-FU $AUC_{0\text{-}46h}$ between 20 and 30 mg*h/L) within two dose cycles of 5-FU. ***Secondary endpoints*** • $AUC_{0\text{-}46h}$ of 5-FU in patients treated with FOLFIRINOX • Incidence of grade ≥ 1-5 toxicity, toxicity-related hospitalization, treatment delay (> 2 days) and early treatment withdrawal in patients treated with FOLFIRINOX. • Pharmacokinetics of 5-FU
PART B • To determine the safety, feasibility and model performance of MIPD of 5-FU in pancreatic cancer patients treated with FOLFIRINOX.	**PART B** ***Primary endpoint*** • Percentage of patients undergoing FOLFIRINOX treated with 5-FU MIPD achieving a 5-FU target AUC range (5-FU $AUC_{0\text{-}46h}$ between 20 and 30 mg*h/L) within two dose cycles of 5-FU. ***Secondary endpoints*** • $AUC_{0\text{-}46h}$ of 5-FU in patients treated with FOLFIRINOX • Incidence of grade ≥ 1-5 toxicity, toxicity-related hospitalization, treatment delay (> 2 days) and early treatment withdrawal in patients treated with FOLFIRINOX. • Pharmacokinetics of 5-FU • Turn-around-time of 5-FU MIPD (or incidence of treatment delay due to 5-FU MIPD) • Compliance to 5-FU MIPD dosing advice by treating physicians

	• Direct medical costs of 5-FU based treatment
Secondary objectives	**Endpoints for secondary objectives**
PART A	**PART A**
• To develop a population PK model of 5-FU for applying 5-FU MIPD in for patients treated with FOLFIRINOX. • To get insights in whether and specifically which limited sampling schedule of 5-FU samples is sufficient to safely adjust 5-FU dosing in routine clinical practice.	• $AUC_{0\text{-}46h}$ of 5-FU in patients treated with FOLFIRINOX
• To identify patient and treatment characteristics correlated with 5-FU exposure/PK (variability) and 5-FU induced toxicity.	• $AUC_{0\text{-}46h}$ of 5-FU in patients treated with FOLFIRINOX • Correlation of patient and treatment characteristics with AUC of 5-FU and/or irinotecan
• To determine the intra-individual variation in 5-FU $AUC_{0\text{-}46h}$ • To determine the inter-individual variation in 5-FU $AUC_{0\text{-}46b}$	• $AUC_{0\text{-}46h}$ of 5-FU in patients treated with FOLFIRINOX
• To determine the incidence of grade 1-5 toxicity, toxicity-related hospital admissions, treatment delay and early treatment withdrawal at 5-FU exposure below, within and above the target window.	• Incidence of grade ≥ 1-5 toxicity, toxicity-related hospitalization, treatment delay (> 2 days) and early treatment withdrawal in patients treated with FOLFIRINOX.
• To determine survival outcomes at 5-FU exposure below, within and above the target window, accounted for stage of disease.	• Disease-free and progression-free survival, objective response rate and overall survival of patients treated with FOLFIRINOX
• To get insights the optimal therapeutic 5-FU exposure range ($AUC_{0\text{-}46h}$) in patients pancreatic cancer treated with FOLFIRINOX.	• $AUC_{0\text{-}46h}$ of 5-FU in patients treated with FOLFIRINOX • Disease-free and progression-free survival, objective response rate and overall survival of patients treated with FOLFIRINOX • Incidence of grade ≥ 1-5 toxicity, toxicity-related hospitalization, treatment delay (> 2 days) and early treatment withdrawal in patients treated with FOLFIRINOX.

PART B	**PART B**
• To determine the percentage of patients that achieves therapeutic (AUC) range of 5-FU defined by an AUC target of 5-FU $AUC_{0\text{-}46h}$ between 20 and 30 mg*h/L when dosed based on 5-FU MIPD.	• $AUC_{0\text{-}46h}$ of 5-FU in patients treated with FOLFIRINOX
• To determine the incidence of grade 1-5 toxicity, toxicity-related hospital admissions, treatment delay and early treatment withdrawal in patients with 5-FU MIPD.	• Incidence of grade ≥ 1-5 toxicity, toxicity-related hospitalization, treatment delay (> 2 days) and early treatment withdrawal in patients treated with FOLFIRINOX.
• To get insights in the preliminary clinical benefit (ORR, OS, PFS) of 5-FU MIPD, accounted for stage of disease.	• $AUC_{0\text{-}46h}$ of 5-FU in patients treated with FOLFIRINOX • Disease-free and progression-free survival, objective response rate and overall survival of patients treated with FOLFIRINOX
• To get insights in the safety and pharmacokinetics of irinotecan dosages in different UGT1A1 genotypes.	• Incidence of grade ≥ 1-5 toxicity, toxicity-related hospitalization, treatment delay (> 2 days) and early treatment withdrawal in patients treated with FOLFIRINOX. • Pharmacokinetics of irinotecan and its metabolite SN-38 in UGT1A1 PMs, IMs and EMs
• To determine the feasibility/turn-around-time of 5-FU model-informed precision dosing defined as no delay of treatment due to 5-FU MIPD.	• Turn-around-time of 5-FU MIPD • Incidence of treatment delay due to 5-FU MIPD) • Direct medical costs of 5-FU based treatment
• To verify the use of 5-FU MIPD by treating physicians in clinical practice for 5-FU dosing.	• Compliance to 5-FU MIPD dosing advice by treating physicians • Reasoning for (not) adhering/using 5-FU of MIPD advice through a small questionnaire to treating physicians
Exploratory objectives	**Endpoints for exploratory objectives**
See text below.	See text below.

4.2 Exploratory objectives

PART A and PART B

5-FU

- To investigate the correlation between the incidence of grade 1-5 toxicity, toxicity-related hospitalization, treatment delay and early treatment withdrawal and the total 5-FU exposure.
- To investigate the correlation between PFS and the total 5-FU exposure.
- To determine the correlation between the baseline endogenous DPD substrate plasma ratios of DHA/U and DHU/T with the pharmacokinetics of 5-FU in patients treated with FOLFIRINOX.
- To get insights in the correlation between DPD activity with 5-FU exposure in the 5-FU dose cycle

Irinotecan

- To establish the population irinotecan, SN-38 and SN-38G AUC distribution of intravenous irinotecan in patients with pancreatic cancer treated with FOLFIRINOX.
- To determine the intra-individual variation in irinotecan, SN-38 and SN-38G AUCs.
- To determine the inter-individual variation in irinotecan, SN-38 and SN-38G exposure.
- To establish the population irinotecan, SN-38 and SN-38G AUC range of intravenous irinotecan in UGT1A1 PM, IM and NM patients with pancreatic cancer treated with FOLFIRINOX.
- To get insights in the frequency and severity of AEs at different irinotecan, SN-38 and SN-38G exposure ranges.
- To get insights in the treatment efficacy (ORR, PFS, OS) at different irinotecan, SN-38 and SN-38G exposure (AUC) ranges.
- To get insights in the optimal therapeutic irinotecan, SN-38 and SN-38G exposure (AUC) range in pancreatic cancer patients treated with FOLFIRINOX.
- To investigate the correlation between incidence of grade 1-5 toxicity, toxicity-related hospitalization, treatment delay and early treatment withdrawal and the total irinotecan, SN-38 and SN-38G exposure (AUC).
- To investigate the correlation between PFS and the total irinotecan, SN-38 and SN-38G exposure (AUC).
- To determine treatment efficacy parameters (ORR, PFS, OS) of irinotecan in UGT1A1 PMs, IMs and NMs with *UGT1A1* genotype-guided dosing.

Oxaliplatin

- To establish the population oxaliplatin free fraction/ultrafiltrate (pUF) AUC in patients with pancreatic cancer treated with FOLFIRINOX.
- To determine the intra-individual variation in oxaliplatin/platinum AUCs.
- To determine the inter-individual variation in oxaliplatin/platinum exposure.

Patient Reported Outcome Measures

- To evaluate patient reported outcome measures (PROMs) at 5-FU exposure below, within and above the target window through PACAP QoL questionnaires.
- To get insights in the preliminary effect of MIPD of 5-FU on the quality-of-life of pancreatic cancer patients through PACAP questionnaires, by comparing patient reported outcome measures in 5-FU BSA-dosed patients (PART A) and in 5-FU MIPD-dosed patients (PART B).

Dry Blood Spot

- To get insights in the reliability of the 5-FU Dry Blood Spot (DBS) analysis by taking Dry Blood DBS samples during 5-FU continuous infusion at the same time points as the venous plasma collection in EDTA (golden standard).

Body composition

- To assess body composition features through body composition parameters in patients with pancreatic cancer treated with 5-FU, using routinely performed contrast-enhanced CT scans in the (portal-) venous phase.
- To establish the population range of body composition features (skeletal muscle mass, visceral adipose tissue mass, subcutaneous adipose tissue mass, radiation attenuation of these tissue compartments) in patients with pancreatic cancer treated with FOLFIRINOX.
- To get insights in the correlation between 5-FU, irinotecan and oxaliplatin exposure and body composition features (skeletal muscle mass, visceral adipose tissue mass, subcutaneous adipose tissue mass and radiation attenuation of these tissue compartments) in pancreatic cancer patients treated with FOLFIRINOX.
- To determine the frequency and severity of AEs for different body composition features in pancreatic cancer patients treated with FOLFIRINOX.
- To get insights in the correlation between body composition features (skeletal muscle mass, visceral adipose tissue mass, subcutaneous adipose tissue mass and radiation attenuation of these tissue compartments) and FOLFIRINOX-induced toxicity in pancreatic cancer patients treated with FOLFIRINOX.

Cost-effectiveness

- To determine whether 5-FU MIPD is cost-saving by performing a cost-analysis using direct medical costs only from a health care payer perspective.

PGx analysis

- To measure and get insights in (novel) germline DNA variant alleles that may be associated with 5-FU, irinotecan or oxaliplatin pharmacokinetics, toxicity and/or efficacy.

Circulating tumor DNA

- To measure circulating tumor DNA in human whole blood in pancreatic cancer patients.
- To get insights in tumor response (sensitivity/resistance) to FOLFIRINOX treatment in pancreatic cancer patients by assessing circulating tumor DNA/markers in human whole blood.
- To get insights in the additional value of liquid biopsies in pancreatic cancer patients as an early biomarker for treatment response.

Microbiome

- To get insights in whether high β-glucuronidase activity is associated with gastrointestinal toxicity and efficacy outcomes.

4.3 Primary endpoint

PART A

- Percentage of patients undergoing FOLFIRINOX treated with standard-dosed (BSA) 5-FU achieving a 5-FU target AUC range (5-FU $AUC_{0\text{-}46h}$ between 20 and 30 mg*h/L) within two dose cycles of 5-FU. *This endpoint is assessed at treatment cycles 1, 2, and in subsequent FOLFIRINOX cycles in which 5-FU dose adjustments (≥15%) are applied*

PART B

- Percentage of patients undergoing FOLFIRINOX treated with 5-FU MIPD achieving a 5-FU target AUC range (5-FU $AUC_{0\text{-}46h}$ between 20 and 30 mg*h/L) within two dose cycles of 5-FU. *This endpoint is assessed at treatment cycles 1, 2, and in subsequent FOLFIRINOX cycles in which 5-FU dose adjustments (≥15%) are applied.*

4.4 Secondary and exploratory endpoints

PART A and PART B

- $AUC_{0\text{-}46}$ of 5-FU in patients treated with FOLFIRINOX
- Incidence of grade ≥ 1-5 toxicity, toxicity-related hospitalization, treatment delay (> 2 days) and early treatment withdrawal in patients treated with FOLFIRINOX
- Disease-free survival, progression free survival, objective response rate and overall survival of patients treated with FOLFIRINOX
- Quality of Life (measured through PACAP questionnaires (EQ-5D-5L, EORTC QLQ C30, EORTC QLQ PAN26, EORTC QLQ CIPN20, Happiness, HADS, WOPS, APECC))
- Turn-around-time of 5-FU MIPD (or incidence of treatment delay due to 5-FU MIPD)
- Compliance to 5-FU MIPD dosing advice by treating physicians
- Reasoning for (not) adhering/using 5-FU of MIPD advice through a small questionnaire to treating physicians
- Pharmacokinetics of 5-FU
- Pharmacokinetics of irinotecan and its metabolite SN-38 and SN-38G in UGT1A1 PMs, IMs and EMs
- Pharmacokinetics of oxaliplatin pUF
- Direct medical costs of 5-FU based treatment
- The minimum number of samples to assess the $AUC_{0\text{-}46h}$ of 5-FU
- AUC contribution of 5-FU bolus infusion in PK model
- Correlation of patient and treatment characteristics with AUC of 5-FU and/or irinotecan
- Body composition features through body composition parameters (skeletal muscle (SM) index in cm/m^2, subcutaneous adipose tissue (SAT) index in cm/m^2, visceral adipose tissue (VAT) index in cm/m^2, radiation attenuation (RA) of SM/SAT/VAT in Hounsfield Units, sarcopenia)

- β-glucuronidase activity of the gut microbiota
- gut microbiota composition, diversity and functional capacity

5. STUDY PLAN AND DESIGN

5.1 Trial Design

Multicentre, non-randomized, pharmacokinetic and intervention study to validate the 5-FU $AUC_{0\text{-}46h}$ target range of the FOLFIRINOX regimen (PART A), and to evaluate the safety and feasibility of a personalized 5-FU MIPD to achieve 5-FU AUC target range exposure (PART B) in pancreatic cancer patients.

5.2 Number of Patients

A total of 100 patients will be included in the PERFUPANC phase-2 trial. The first 50 patients will be included in PART A, and the second 50 patients will be included in PART B.

5.3 Overall study duration and follow-up

The planned duration of this trial is 3 years, from September 2024 to September 2027, based on the number of pancreatic cancer patients that started with FOLFIRINOX in the Catharina Hospital Eindhoven, Isala Hospital Zwolle, Amsterdam UMC, LUMC, and EMC in 2022-2023. Patients will be followed for e.g. toxicity and efficacy during treatment, and after completion of their last treatment cycle of FOLFIRINOX will be followed-up until disease progression or death. Follow-up ends when the last patient from part B has received their last treatment cycle of FOLFIRINOX.
For PART A, it is expected that 50 patients will be included from September 2024 to September 2025. The planned duration of PART A data analysis, 5-FU PK model development and implementation into InsightRX is 4 months. PART B may be initiated after the 5-FU PK/MIPD model is implemented and is therefore expected to be initiated January 2026. For PART B, it is expected that 50 patients will be included from February 2026 to February 2027. Based on 6 months FOLFIRINOX treatment, follow-up is expected to be finalized in September 2027. The planned duration of final data analysis (PART A and PART B) and completion of the final study report is 6 months.

5.4 Patient participation

In the PERFUPANC phase-2 study, we want to involve the patient perspective at an early stage of the study as we are convinced that patient participation in the design and implementation phase of our study is essential to guarantee relevance, feasibility and quality of PERFUPANC. Therefore we have established collaboration with the pancreatic cancer patient organization “Living With Hope” (LWH). A representative from LWH (board member of LWH, member of the Patient Advisory Council of IKN, pancreatic cancer patient undergoing FOLFIRINOX treatment). The representative has been consulted for their own experience and into their insights in the pancreatic cancer patient group. During the design for the PERFUPANC phase-2 study, they have advised us from the patient perspective in the areas of:

- *Identifying research needs in line with PERFUPANC;*
- *Prioritizing research questions;*

- *Helping choose outcome variables/method of data collection (incl. assessing the burden).*

They have also provided us with feedback on the research protocol and together we are working on bringing a 'klankbordgroep' together for the PERFUPANC phase-2 study.

LWH has given us input regarding recruitment and informing potential participants and drafting comprehensible patient information letters (ICFs).

We plan on continuing patient participation during the trial stages of implementation, intervention, evaluation and dissemination, with LWH, as well as with Patient Councils of the Catharina Cancer Institute. Patient organizations/representatives are involved in PERFUPANC in an informing, consulting and/or advising role.

6. STUDY POPULATION

6.1 Population

The study population consist of pancreatic cancer patients undergoing FOLFORINOX chemotherapy at Catharina Hospital Eindhoven, Amsterdam UMC, Leiden University Medical Centre, Isala Hospital Zwolle, Erasmus Medical Centre. A minimum of 25 PC patients in the advanced setting will be included for both PART A and PART B to be able to perform comparison analyses between the study cohorts from PART A and B. For PART A, a minimum of 15 patients with classic FOLFIRINOX regimen and 15 patients with modified FOLFIRINOX regimen will be included for adequate pharmacokinetic assessments of both groups.

6.2 Inclusion criteria

In order to be eligible to participate in PART A and PART B of this study, a subject must meet all of the following criteria:

1. Pathologically confirmed pancreatic cancer diagnosis;
2. Patient scheduled to start FOLFIRINOX treatment;
3. Patient with age ≥ 18;
4. Patient is able and willing to give written IFC;
5. Patient is able and willing to undergo extra blood sampling for 5-FU analysis.
6. WHO performance status 0-2.

6.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

1. Patients with known substance abuse, psychotic disorders, and/or other diseases expected to interfere with study or patient's safety.
2. Patients with *DPYD* gene-activity score 0 and 0.5.

6.4 The role of pregnancy and contraceptive care

Conform standard care, patients should avoid unprotected sex to avoid becoming pregnant or making their partner become pregnant while having chemotherapy. Therefore, the same applies to participants in the current study. Participants/patients discuss fitting contraceptive care as part of standard care with their treating physician. Patients that are pregnant or are breastfeeding are not allowed to participate in the current study. If a study subject becomes pregnant during participation in the current study, the treating physician is informed and the study subject will be discontinued from the current study.

7. STUDY TREATMENTS

7.1 Investigational Medicinal Product(s) (IMP(s))

7.1.1 Name and description of the IMP

The investigational products in this study are 5-FU, irinotecan and oxaliplatin. See Summaries of Product Characteristics (SPC) of 5-FU, irinotecan (CPT-11) and oxaliplatin. These are part of the modern regimen which is already applied in current standard care. The chemotherapeutic drug 5-FU, will be the main focus of this study.

The chemotherapeutic drugs will be administered on day 1 to 3 of a two weeks cycle. The intended duration of the therapy is 12 cycles. It is common that the number of cycles differ in patients due to toxicity. The chemotherapeutic drugs used FOLFIRINOX chemotherapy can be found in Tables 3 and 4. More detailed information about procedures (e.g. timing and flushing) can be found in the protocol (Appendix III and IV). Local protocols will be used at each participating center for the FOLFIRINOX regimen (comedication/prophylactic medication) and patient information, as FOLFIRINOX is a standard regimen and minor differences in this will not affect the current study. The local protocol of Catharina Hospital Eindhoven has been included in Appendix I and II as an example of such a protocol. Minor differences in local protocols between sites are expected in used premedication and 5-FU continuous system of choice, and are not expected to impact endpoint parameters. For FOLFIRINOX administration, the same protocol will be used by all centers (Appendix III and IV).

Table 3. The treatment protocol of classic FOLFIRINOX

Medication	**Day 1**	**Day 2**	**Day 3**	**Day 4 – 14**	**Administration route (hours)**	**Dosage (mg/m2)**
Irinotecan	x			Rest	iv (1h30min)	180
Oxaliplatin	x				iv (2h)	85
Leucovorin	x				iv (15min)	400
Fluorouracil	x				iv (5 min)	400
Fluorouracil	x	x	x		iv (46h)	2400

Table 4. The treatment protocol of mFOLFIRINOX

Medication	**Day 1**	**Day 2**	**Day 3**	**Day 4 – 14**	**Administration route (hours)**	**Dosage (mg/m2)**
Irinotecan	x			Rest	iv (1h30min)	150
Oxaliplatin	x				iv (2h)	85
Leucovorin	x				iv (15min)	400
Fluorouracil	x	x	x		iv (46h)	2400

Cycle 1 and 2 are chosen to obtain blood samples to reduce the burden for the patients. Additionally, in subsequent cycles where a patient may receive a 5-FU dose adjustment (≥15%) blood samples will also be obtained.

If a patient is unwilling to undergo blood sampling for irinotecan/oxaliplatin, or unwilling to undergo blood sampling on day 3, the patient can still be included for 5-FU sampling or sampling on day 1 of the treatment cycle.

7.1.2 Status of development of the IMP

Classic and modified FOLFIRINOX are standard 5-FU combination therapies in pancreatic cancer.

5-FU has been tested in many in vitro, animal and ex-vivo human cell material before. It is already considered to be safe and therefore it is now authorised and widely used to treat a variety of cancers. See summary of Product Characteristics (SPC) of 5-FU.
Irinotecan has been tested in many in vitro, animal and ex-vivo human cell material before. It is already considered to be safe and therefore it is now authorised widely used to treat a variety of cancers. See summary of Product Characteristics (SPC) of irinotecan (also known as CPT-11).
Oxaliplatin has been tested in many in vitro, animal and ex-vivo human cell material before. It is already considered to be safe and therefore it is now authorised widely used to treat a variety of cancers. See summary of Product Characteristics (SPC) of oxaliplatin.
Leucovorin: Leucovorin infusion that patients receive during this study are part of the regimens in current standard care. See summary of Product Characteristics (SPC) of leucovorin.

7.1.3 Description and justification of dosage and route of administration

For the classic FOLFIRINOX regimen, the standard 5-FU doses consist of 5-FU bolus infusion of 400 mg/m² and 5-FU continuous infusion of 2400 mg/m². The standard irinotecan dose consists of an irinotecan infusion of 180 mg/m². The standard dose of oxaliplatin consists of an oxaliplatin infusion of 85 mg/m².
For the mFOLFIRINOX regimen, the standard 5-FU dose consists only of a 5-FU continuous infusion of 2400 mg/m². The standard irinotecan dose consists of an irinotecan infusion of 180 mg/m². The standard dose of oxaliplatin consists of an oxaliplatin infusion of 85 mg/m².

For PART A, 5-FU, irinotecan and oxaliplatin are dosed as routine standard-of-care.
5-FU is dosed on BSA and *DPYD* genotype. Irinotecan is dosed on BSA and *UGT1A1* genotype as standard of care. *DPYD* and *UGT1A1* genotyping is standard practice on the location CZE, Amsterdam UMC, LUMC, Isala and EMC.
Oxaliplatin is dosed on BSA as standard of care. Dose reductions can be done in case of dose limiting toxicity or dose escalations due to good tolerability can be done according to standard guidelines and left to the discretion of the treating oncologist.
Detailed information of regimen, dosage and duration of the chemotherapy is described in the protocol (Appendix I-IV).
Dose reductions can be done in case of dose limiting toxicity or dose escalations due to good tolerability can be done according to standard guidelines and left to the discretion of the treating oncologist.

For PART B, irinotecan and oxaliplatin are dosed as routine standard-of-care (see above).
For 5-FU, dose reductions and escalations according to our developed 5-FU Pop-PK/MIPD model will be applied on both the 5-FU bolus infusion as well as the 5-FU continuous infusions. The initial dose of 5-FU depends patient and treatment characteristics (e.g. BSA, and *DPYD* genotype, age, sex, organ function, co-medication…) of the patient and is calculated with the 5-FU Pop-PK/MIPD model to reach the target AUC window of 5-FU. After cycle 1, the 5-FU doses will be adjusted based on $AUC_{0\text{-}46h}$ of 5-

FU and toxicity. The anticipated target AUC window of 5-FU is between 20 and 30 mg*h/L. More detailed information about 5-FU dose adjustment can be found in section 10.3.10.

The oncologist interprets the dose advice provided by the pharmacist (that is based on calculated AUC by the 5-FU MIPD model) and decides whether this dose advice will be used considering the clinical status of the patient and previous toxicity. Furthermore, oncologist may also delay or discontinue chemotherapy when patients experience severe toxicity.

The dose of 5-FU, irinotecan and oxaliplatin, which is prescribed, prepared and administered to the patient is documented in the electronic patient record HiX/EPIC.

All chemotherapeutic agents will be administered intravenously.

7.2 Comparator IMP(s)

Not applicable.

7.3 Placebo

Not applicable.

7.4 Auxiliary Medicinal Product(s) (AxMP(s))

7.4.1 Name and description of the AxMP

Not applicable.

7.4.2 Statement on authorisation and justification unauthorised AxMP (if applicable)

Not applicable.

7.4.3 Description and justification of dosage and route of administration

Not applicable.

7.5 Additional considerations for trials involving a medical device

In PART B of this study, the develop population PK model will be used as a tool for personalized and precise 5-FU dosing advice based on 5-FU $AUC_{0\text{-}46h}$. This so-called model-informed precision dosing (MIPD) will be implemented and used under Insight Rx Nova software for MIPD of 5-FU in PART B, which is within the scope of its intended use. Because of this aspect of the study, PART B of the study is characterized to fall under the scope of the Medical Device Regulation article 82.

Insight Rx Nova specifications

InsightRX Nova (PK) software is currently available in the EU as a Class I medical device under the MDD regulation CE Mark. The InsightRX NovaTM software conforms to ISO13485, IEC 62304, ISO 14971, ISO 14155, IEC 62366-1, 21 CFR Part 11, and GxP.
Current software version: WebApp: 1.43.6 / R-API: 1.43.3 / 2023
Manufacturer: InsightRx, Inc. 548 Market Street, #88083, San Francisco, CA 94104 USA / support@insight-rx.com / +1 (205) 351 0574 / https://www.insight-rx.com

Authorized European Representative: CMC Medical Devices & Drugs, S.L. / C/ Horacio Lengo n18, C.P 29006 Málaga-Spain
Importer: MedEnvoy / Prinses Margrietplantsoen 33 - Suite 123, 2595 AM The Hague The Netherlands
Instructions for Use: 320-00201-DO-01 Rev 8, 03/23

The Intended Use of InsightRX Nova (PK) software is stated by the manufacturer as follows:

PRODUCT DESCRIPTION

The InsightRX NOVA software is a cloud-based Clinical Decision Support tool with application to Therapeutic Drug Monitoring of various selected therapeutic drugs. The Nova platform is available in a standalone version accessible through the website nova-eu.insight-rx.com. Nova's precision dosing modules are based on published, peer-reviewed, clinically validated population pharmacokinetic (PK) models. Maximum a posteriori (MAP) Bayesian estimation methodology is used to calculate an individual patient's PK parameters (clearance, volume of distribution, etc.) and leverage the individualized estimates to forecast the patient's drug concentration time course. In addition to MAP Bayesian estimations, the platform also provides options to perform least-squares estimation and various other methods for PK parameter estimations. The InsightRX platform allows the user to assess and visualize dosing regimens based on comprehensive PK knowledge about the patient to optimize dosing and achieve a desired therapeutic target (AUC, Ctrough, Cmax etc.).

INTENDED MEDICAL INDICATION

The software is intended to support PK/PD analysis for various specified drugs and disease indications with the ultimate to increase safety (i.e. reduce adverse events) and efficacy of treatment by optimizing systemic drug exposure.

INTENDED USE

The InsightRX Nova software is intended for use by trained healthcare practitioners to calculate and analyze individual patient PK/PD characteristics and perform real-time PK/PD simulations. The software allows the user to assess and visualize the drug concentration time course based on user selected dosing regimens. The user can calculate, and review dosing recommendations based upon user provided clinical exposure targets (e.g. AUC, Ctrough, Cmax) using the software.

INDICATIONS FOR USE

The InsightRX Nova software is indicated to generate simulations using published or user-defined PK/PD models of specified drugs in a hospital setting. Trained healthcare professionals may use the simulations as adjunct information to help make treatment decisions for the patient to increase safety and efficacy of treatment.

InsightRX Nova (PK) for MIPD of 5-FU within scope of intended use

In the current study InsightRX Nova will be used for Bayesian dosing/TDM of 5-FU, analyze individual patient 5-FU PK/PD characteristics and perform real-time 5-FU PK/PD simulations. We will develop a 5-FU PopPK model based on the PART A dataset and available 5-FU PopPK models in literature. Our PopPK model/MIPD algorithm will then be implemented in the InsightRX Nova software for use of MIPD of 5-FU in PART B. InsightRX allows users to calculate, and review dosing recommendations based upon user provided clinical exposure targets (e.g. AUC, Ctrough, Cmax) and Pop-PK models using

the software. Our model within InsightRX will only be used by trained healthcare practitioners. Therefore, MIPD of 5-FU within Insight RX Nova software is in accordance with its intended use.

7.6 Additional considerations for trials involving an in-vitro diagnostic or companion diagnostic

Not applicable.

7.7 Preparation and labelling of the study treatment(s)

5-FU, irinotecan and oxaliplatin infusions will be prepared in the hospital pharmacy from 5-FU, irinotecan and oxaliplatin vials and labelled according to local procedures. The vials are a registered pharmaceutical product, that are GMP produced by the marketing authorization holder. Storage of the vials in the pharmacy is according the SPC in temperature-controlled environment in compliance with GDP. Because of the teratogenic nature of 5-FU, irinotecan, and oxaliplatin, vials will not be delivered to the medical staff and the patients. Therefore no additional labels will be used in this study.

8. OTHER TREATMENTS AND RESTRICTIONS

8.1 Concomitant therapy

All concomitant medications are allowed, but conform the SPCs of 5-FU, irinotecan, oxaliplatin and leucovorin.

8.2 Lifestyle restrictions

Conform SPCs of 5-FU, irinotecan, oxaliplatin and leucovorin.

9. TRACEABLILITY, STORAGE, ACCOUNTABLILITY AND COMPLIANCE

9.1 Traceability and storage of the study treatment(s)?

All treatments used in the current study are authorized IMPs. 5-FU, irinotecan, oxaliplatin and leucovorin infusions will be prepared in the hospital pharmacy from vials and labelled according to local standardized procedures. The 5-FU, irinotecan, oxaliplatin and leucovorin vials are a registered pharmaceutical product, that are GMP produced by the marketing authorization holder. Storage of the vials in the pharmacy is according the SPC in temperature-controlled environment in compliance with GDP.

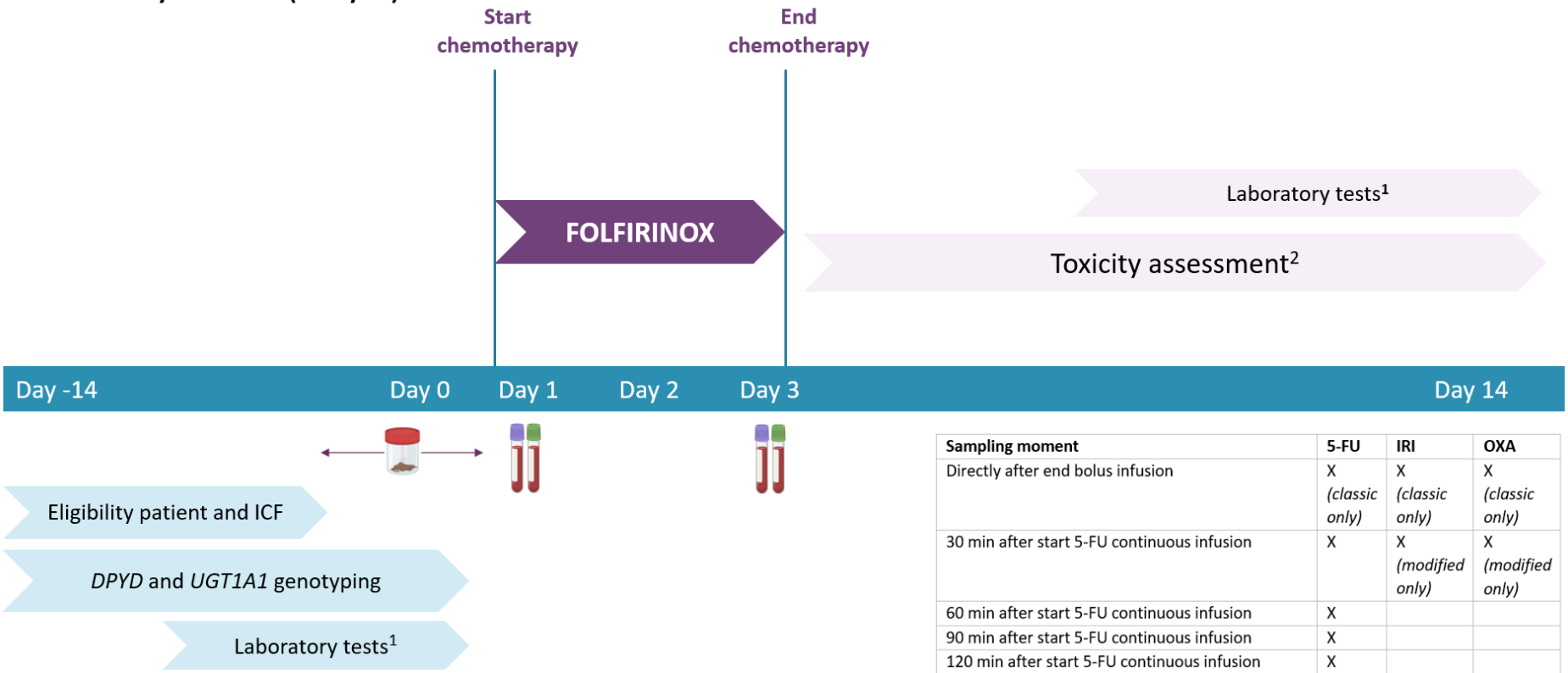
9.2 Accountability of the study treatment(s) and compliance

No formal drug accountability will be performed in this study. The 5-FU, irinotecan, oxaliplatin and leucovorin vials are a registered pharmaceutical product and will be used and discarded in the hospital pharmacy. Identity and expiry will be checked and batch numbers will be registered on the patient specific production sheets, thereby ensuring traceability. The dose, which is prescribed, prepared and administered to the patient is documented in HiX/EPIC.

10. STUDY ASSESSMENTS AND PROCEDURES

A study flowchart is depicted in Figures 6-10.

PART A: Study flowchart (1st cycle)

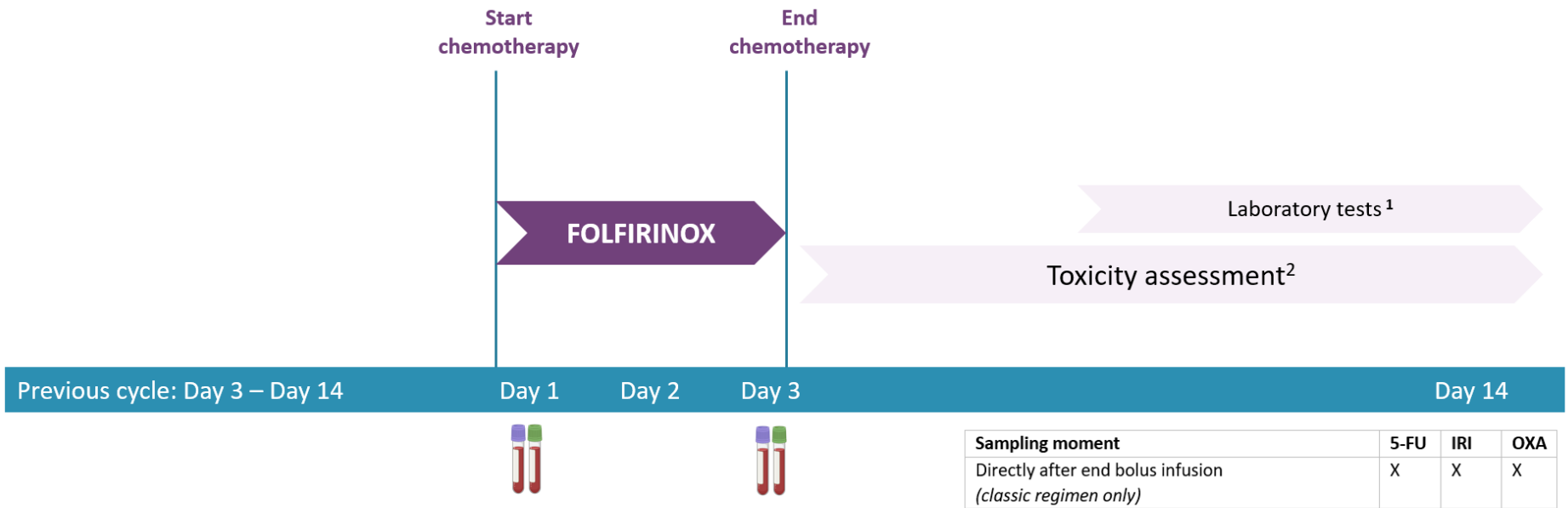


Sampling moment	5-FU	IRI	OXA
Directly after end bolus infusion	X *(classic only)*	X *(classic only)*	X *(classic only)*
30 min after start 5-FU continuous infusion	X	X *(modified only)*	X *(modified only)*
60 min after start 5-FU continuous infusion	X		
90 min after start 5-FU continuous infusion	X		
120 min after start 5-FU continuous infusion	X		
Before end of 5-FU continuous infusion (day 3)	X	X	

1 Complete blood count, bilirubin, creatinin, etc. analysed on the day or few days (1-3 days) before treatment.
2 Toxicity assessment according to the guidelines from the National Cancer Institute (NCI-CTC AE version 5.0).

Figure 6: Study flowchart PART A, first cycle

PART A: Study flowchart (2nd cycle and cycles with 5-FU dose adjustments)

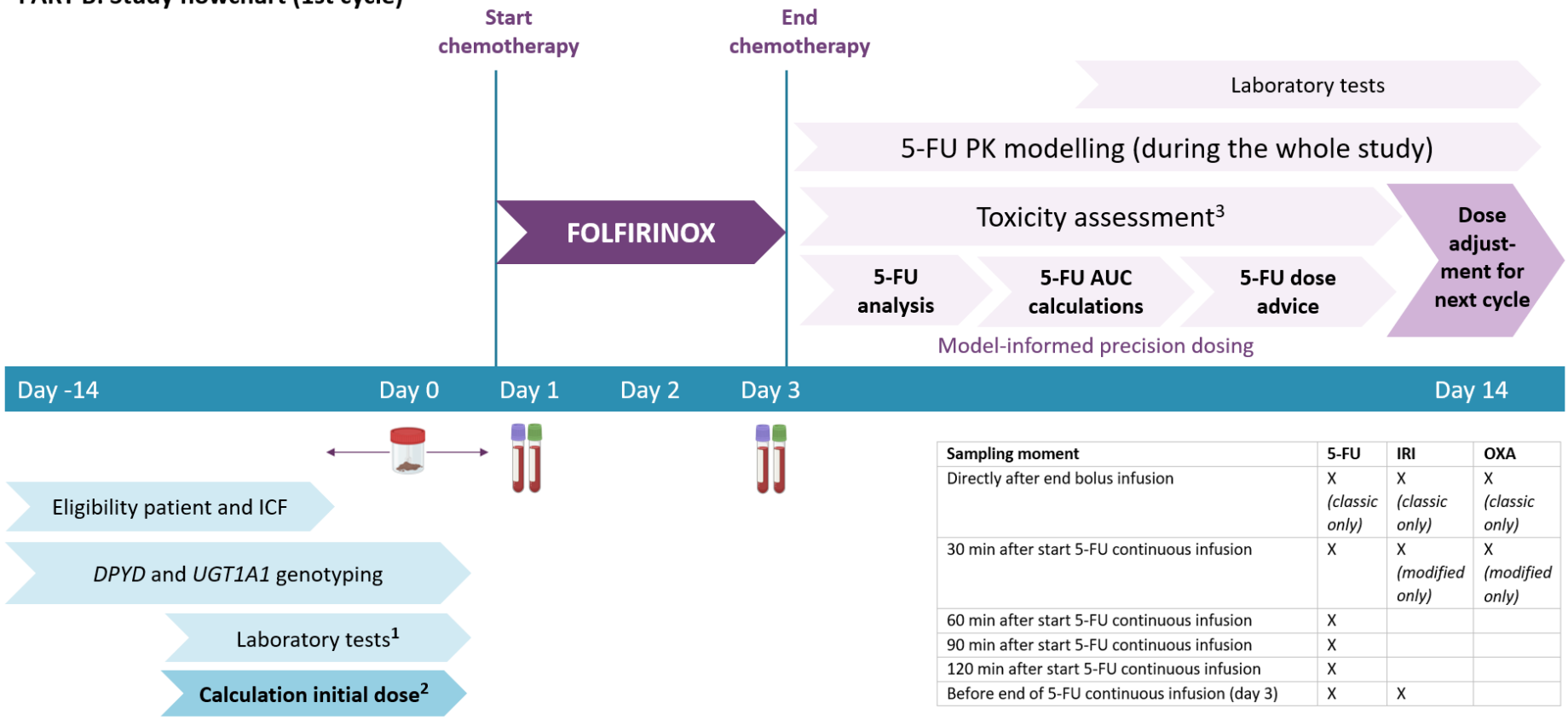


Sampling moment	5-FU	IRI	OXA
Directly after end bolus infusion *(classic regimen only)*	X	X	X
30 min after start 5-FU continuous infusion *(modified regimen only)*	X	X	X
120 min after start 5-FU continuous infusion	X		
Before end of 5-FU continuous infusion (day 3)	X	X	

1 Complete blood count, bilirubin, creatinin, etc. analysed on the day or few days (1-3 days) before treatment.
2 Toxicity assessment according to the guidelines from the National Cancer Institute (NCI-CTC AE version 5.0).

Figure 7: Study flowchart PART A, second cycle and cycles with 5-FU dose adjustments (≥15%).

PART B: Study flowchart (1st cycle)

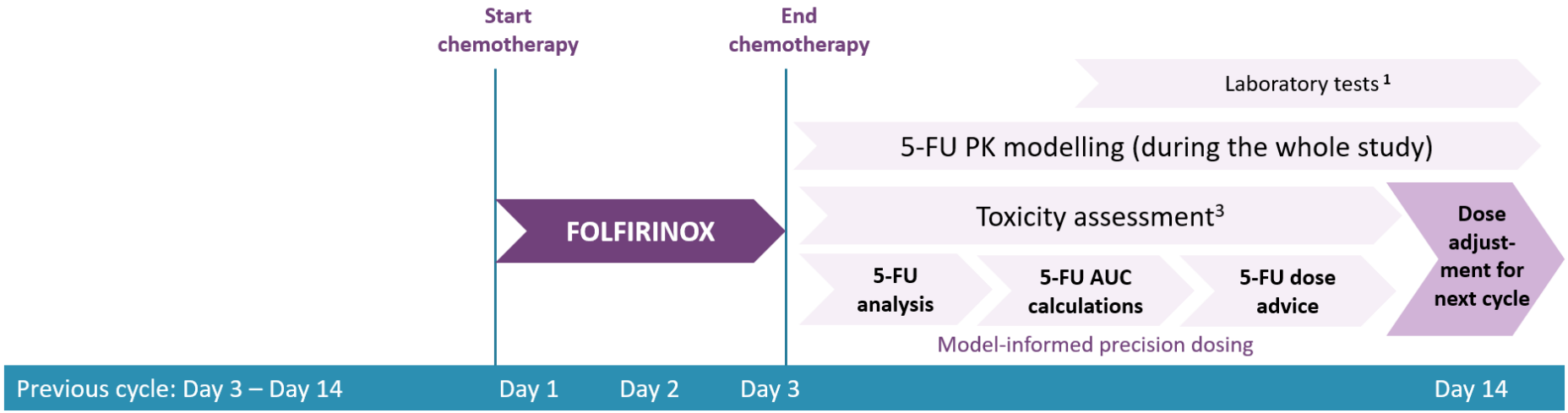


Sampling moment	5-FU	IRI	OXA
Directly after end bolus infusion	X *(classic only)*	X *(classic only)*	X *(classic only)*
30 min after start 5-FU continuous infusion	X	X *(modified only)*	X *(modified only)*
60 min after start 5-FU continuous infusion	X		
90 min after start 5-FU continuous infusion	X		
120 min after start 5-FU continuous infusion	X		
Before end of 5-FU continuous infusion (day 3)	X	X	

1 Complete blood count, bilirubin, creatinin, etc. analysed on the day or few days (1-3 days) before treatment.
2 Initial dose is based on patient characteristics (among which hepatic and renal function (bilirubine, GFR, etc.), BSA, *UGT1A1 genotype and DPYD* genotype or DPD phenotype) and calculated with MIPD algorithm to reach target AUC range
3 Toxicity assessment according to the guidelines from the National Cancer Institute (NCI-CTC AE version 5.0).

Figure 8: Study flowchart PART B, first cycle.

PART B: Study flowchart (2nd cycle and cycles with 5-FU dose adjustments)

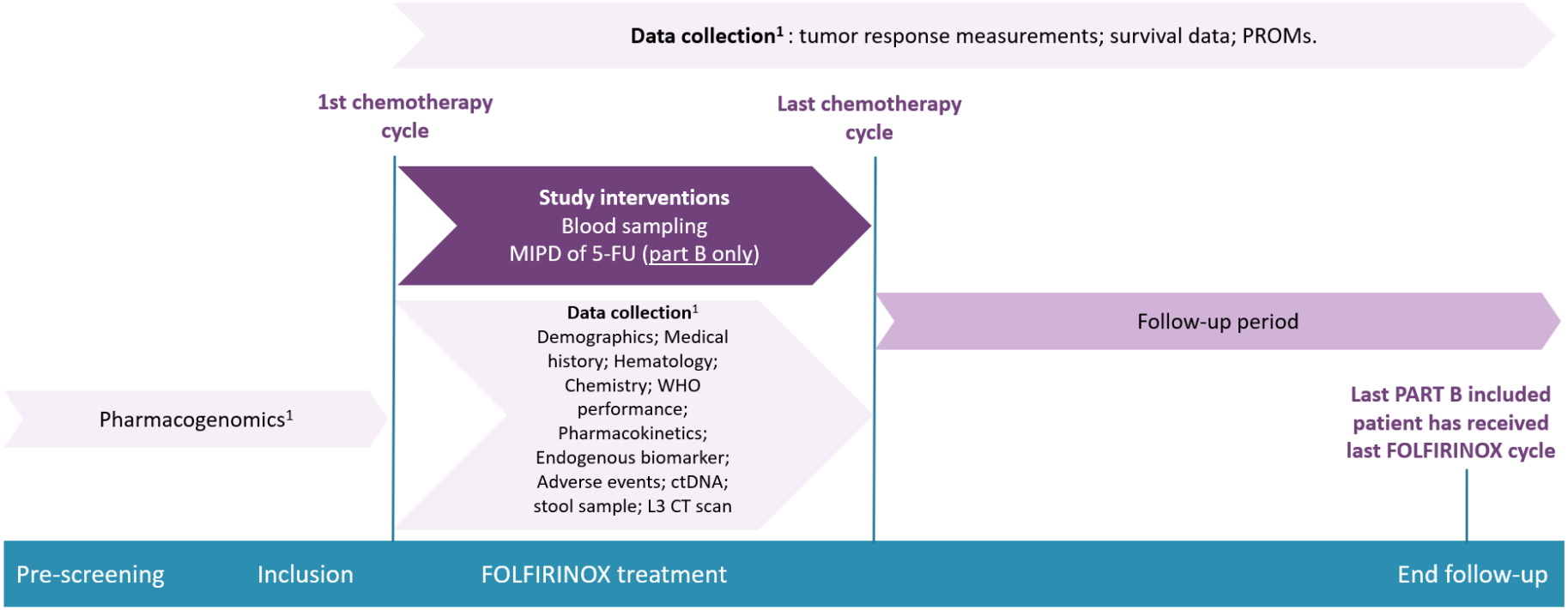


Sampling moment	5-FU	IRI	OXA
Directly after end bolus infusion *(classic regimen only)*	X	X	X
30 min after start 5-FU continuous infusion *(modified regimen only)*	X	X	X
120 min after start 5-FU continuous infusion	X		
Before end of 5-FU continuous infusion (day 3)	X	X	

1 Complete blood count, bilirubin, creatinin, etc. analysed on the day or few days (1-3 days) before treatment.
2 Dose is based on 5-FU AUC and patient characteristics; individual dose is calculated with MIPD algorithm to reach target AUC range and based on toxicity profile from previous cycle
3 Toxicity assessment according to the guidelines from the National Cancer Institute (NCI-CTC AE version 5.0).

Figure 9: Study flowchart PART B, second cycle and cycles with 5-FU dose adjustments (≥15%).

Follow-up: Study flowchart (PART A and PART B)



1 See section 10.3 and table 5 for details.

Figure 10: Study flowchart PART and PART B, collection of patient blood samples and data. FOLFIRINOX treatment is defined as the period in which a participant receives FOLFIRINOX treatment cycle(s). After this period, the participant no longer receives FOLFIRINOX treatment and is only followed-up for additional data collection.

10.1 Screening procedure

PART A and PART B

Patients diagnosed for pancreatic cancer and planned for FOLFIRINOX treatment at the Catharina Hospital Eindhoven, Leiden University Medical Centre, Amsterdam University Medical Centre, Isala Hospital, Erasmus Medical Centre will be recruited and informed of the PERFUPANC phase-2 study at the medical oncology consultation before start of the first cycle of FOLFIRNOX. Electronic patient records are screened by study personnel with a treating relationship (WGBO) to determine what patients are eligible for the study by review of the in- and exclusion criteria. Potential participants will be identified by their treating oncologist. Potential participants will be attended about the existence of the study by their treating physician (oncologist) and will be given the patient information / informed consent form on paper by their treating physician (oncologist). The treating physician will inform a study-investigator about the potential study participant. Investigators will contact the potential study participant to further explain the study and answer the potential participant's questions. Potential participants will be given sufficient time to consider participating in the trial (at least 7 days). Subjects who decide to participate will sign and date the informed consent form (ICF) on paper. The study subject will bring the signed ICF to their hospital for signing of the ICF by a study-investigator. Study procedures may only start after complete signing of the ICF by both parties.

10.2 Randomisation, blinding and treatment allocation

PART A and PART B

Not applicable.

10.3 Study procedures and assessments

PART A and PART B

The follow-up schedule (Table 5) summarizes the minimal observations required for each patient. Additional parameters and/or increased frequency of observations may be required at the treating physician's discretion and according to current standard of treatment and the toxicities observed.

Table 5. Study procedures

Procedure	**Pre-screening**	**Baseline**	**Cycle 1**	**Cycle 2**	**Cycle 3-12**	**Cycles 2+ with 5-FU dose adjustments (≥15%)**
Signing of ICF		x				
Demographics[1]		x	x	x	x	x
Medical history[2]		x				
Hematology[3]		x	x	x	x	x
Chemistry[4]		x	x	x	x	x
WHO Performance status		x	x	x	x	x
Pharmacokinetics			x[5]	x[6]		x[6]
Endogenous biomarker DHU/U and DHU/T		x[7]				
Pharmacogenomics[8]	x					
Adverse events[9]			x	x	x	x
ctDNA[10]		x			x	
Stool sampling[11]		x				
PROMs	~every 3 months via PACAP QoL questionnaires.					
Tumour measurements/CT scans follow-up	As routine clinical practice every ~2 months.					

1. Age, sex, ethnic origin, height in cm, body weight, WHO performance status
2. Current stage of cancer, previous cancer treatments, CT scans at diagnosis, ongoing toxicities related to previous therap(y)(ies), other signs and symptoms present at screening.
3. CBC; haemoglobin, white blood cell count, ANC, neutrophils, leukocytes, platelets
4. Sodium, potassium, serum creatinine, AST, ALT, bilirubin
5. Blood samples will be obtained in all included patients at 6 time points (in total 6x EDTA tube, 4 mL and 3x lithium heparin tube, 4 mL). DBS sampling will be done at 2 time points for the first 25 patients of PART A. See APPENDIX VI.
6. Blood samples will be obtained in all included patients: 3 time points (in total 3x EDTA tube, 4 mL and 3x lithium heparin tube, 4 mL). DBS sampling will be done at 2 time points. See APPENDIX VI.
7. Blood samples for endogenous biomarker concentrations of uracil/DHU and DHU/T will be obtained before start of chemotherapy at these study cycles (1x EDTA tube, 4 mL). See APPENDIX VI.
8. *DPYD* and *UGT1A1* genotyping. The total 10 mL of EDTA blood that has been obtained for the routinely performed *DPYD and UGT1A1* genotyping test may later in retrospect be used for additional pharmacogenetic analyses.
9. Grade and duration according to NCI CTCAE version 5.0.
10. A blood sample (1x10ml EDTA tube or streck tube) for circulating tumor DNA will be obtained before start of chemotherapy. At standard-of-care follow up moments for CT scans (~every 3 months), a blood sample (1x10ml EDTA tube or streck tube) will be taken to later in retrospect be used for additional ctDNA analyses.
11. A fecal sample will be collected prior to the first cycle, or otherwise during the first three days of FOLFIRINOX by the patient, using a patient-friendly, easy-to-use collection kit. Two tubes are filled at one timepoint by the patient. Samples are stored in the freezer until the patient can bring the sample to the next hospital visit. Fecal samples will be stored in the local study site until analysis.

10.3.1 *DPYD* and *UGT1A1* genotyping / pre-screening

PART A and PART B

DPYD and *UGT1A1* genotyping will be performed in all PERFUPANC study patients.

In patients eligible for treatment with 5-FU and irinotecan infusion, the polymorphic status of *DPYD* and *UGT1A1* will be determined according to standard of care. To this purpose a total of 10ml of EDTA blood will be obtained. In addition, another sample of 4 ml will be taken for

obtaining uracil/DHU and thymine/DHU. *DPYD* genotyping is standard procedure in current clinical practice to determine the initial dose of 5-FU. DPD phenotyping by measuring uracil/DHU and thymine/DHU is not standard of care but will be performed at baseline as surrogate biomarker for DPD enzyme activity and exploratory objectives. In PART A, for patients with *DPYD* variants 5-FU will be dosed according to DPWG (Appendix V) and/or local treatment guidelines. In PART B, patients will be dosed based on 5-FU MIPD and the DPWG guideline.
UGT1A1 genotyping is standard procedure in current clinical practice to determine the initial dose of irinotecan. In PART A and B, irinotecan will be dosed according to the DPWG irinotecan guideline (Appendix V).

10.3.2. Standard laboratory examination

PART A and PART B

Standard laboratory assessments are also used to investigate whether patients were eligible to start or continue with chemotherapy. Therefore, regular blood sampling (8 ml) is performed on the day or few days before patients start their cycle. The oncologist decides whether patients are eligible to start or continue with the chemotherapy based on hematological and clinical chemistry values and toxicity assessment of the patient.
The information on patient's hepatic and renal function is important since this may affect the pharmacologic condition of chemotherapeutic drugs used in this study. This information will be documented in HiX/EPIC and extracted for analysis

10.3.3. Baseline assessments

PART A and PART B

Baseline assessments must be performed as close to trial start as possible and the interval must not exceed 7 days, except for radiological tumor assessments, where a period of 4 weeks is permitted.

The following will be obtained at screening:

- Demographic data: age, ethnic origin, sex, height in cm, body weight in kg, WHO performance status
- Medical history: tumor type and tumor markers, current stage of cancer, previous cancer treatments, and symptoms present at screening, L3 CT scan from diagnosis
- Haematology: haemoglobin, white blood cell count, ANC, neutrophils, leukocytes, platelets
- Chemistry: sodium, potassium, ASAT, ALAT, LDH, total bilirubin, albumin, creatinine, and creatinine clearance (calculated as MDRD or CKD-EPI), DHU/U and DHU/T

10.3.4. Assessments during treatment cycles

PART A and PART B

The following assessments will be done prior to each cycle (up to two days before administration):

- Body weight in kg
- L3 CT scan from standard-of-care follow-up
- Relevant comedication: use of atropine and G-CSF
- Haematology: haemoglobin, white blood cell count, ANC, neutrophils, leukocytes, platelets

- Chemistry: sodium, potassium, ASAT, ALAT, LDH, total bilirubin, albumin, creatinine, and creatinine clearance (calculated as MDRD or CKD-EPI)
- Pharmacokinetic analysis of 5-FU, irinotecan, SN-38, SN-38G and free oxaliplatin
- Use of atropine and/or G-CSF
- Adverse events: ongoing toxicities related to previous cycles, other signs and symptoms according to the National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE v4.03) (see appendix VII)
- Efficacy: CA 19-9, ORR, DFS, PFS, OS
- PROMs, QoL
- Beta-glucuronidase activity and gut microbiota composition, diversity and functional capacity from fecal samples (prior to cycle 1 only).

10.3.5. Follow-up assessments after treatment cycles

PART A and PART B

- Efficacy: ORR, DFS, PFS, OS
- PROMs, QoL

10.3.6. Pharmacokinetic sampling of 5-FU, irinotecan and oxaliplatin plasma concentration analysis

PART A and PART B

The blood sampling moments for pharmacokinetic analysis are listed below in table 6 and 7. See also Appendix VI.

Table 6. Sampling strategy for cycle 1 in PART A and PART B

Sampling moment	**5-FU**	**IRI**	**OXA**
Directly after end bolus infusion	X *(classic only)*	X *(classic only)*	X *(classic only)*
30 min after start 5-FU continuous infusion	X	X *(modified only)*	X *(modified only)*
60 min after start 5-FU continuous infusion	X		
90 min after start 5-FU continuous infusion	X		
120 min after start 5-FU continuous infusion	X		
Before end of 5-FU continuous infusion (day 3)	X	X	

Table 7. Limited sampling strategy for cycle 2 and cycles with dose adjustments in PART A and PART B

Sampling moment	**5-FU**	**IRI**	**OXA**
Directly after end bolus infusion *(classic regimen only)*	X	X	X
30 min after start 5-FU continuous infusion *(modified regimen only)*	X	X	X
120 min after start 5-FU continuous infusion	X		
Before end of 5-FU continuous infusion (day 3)	X	X	

Only during the first cycle, six 5-FU blood samples (4 ml) will be obtained from patients. The number of blood samples is reduced from six blood samples in the first cycle to three blood samples in cycle 2 and subsequent cycles with 5-FU dose adjustments (≥15%). After PART A dataset analysis, the 5-FU blood samples for PART B may be reduced to a limited sampling strategy of three blood samples for the first cycle as well. These times of blood sampling were chosen for two reasons. These times are practically feasible for the patient to minimize the burden of the patients. The patient starts the FOLFIRINOX treatment between 11:00 AM – 13:00 PM in the morning. After the irinotecan, oxaliplatin and leucovorin, the patient starts the 5-FU infusion between 13:30 – 15:30 PM. The patient will have to stay in the hospital for 2 hours for a blood draw till approximately 15:30-17:30 PM. Thereafter the patient can go home to return at the hospital two days later between approximately 8:00 - 10:00 AM for the last blood sample just before the end of infusion. The burden of the patient is limited and there is margin until the end of the infusion so that the infusion has not already been run in before the blood sample is drawn. Beumer et al. indicates not to take blood samples in the last 30 minutes of infusion, because the pumps may not run for as long as 46 hours (20). In this study, cassettes are used for 5-FU infusion. These cassettes are connected to and driven by an electric pump. These electric pumps have a more consistent run-in time than the easypumps which have much more run-in time variation. For irinotecan/SN-38, a sample around 49.5 hours after start infusion irinotecan need to be measured as limited sampling time point for assessment of the AUC. Second, the circadian rhythm of DPD activity was taken into account. Variability in 5FU Css should be minimized due to circadian effects. Beumer et al. indicates that the impact of this is relatively small between 06:00 AM and 03:00 PM (+/- 20%); the time span in which we will measure the last samples (20). Therefore we will measure the last 5-FU and irinotecan sample approximately 40-45h after start 5-FU infusion (on day 3) by taking blood samples around approximately 8:00 AM - 01:00 PM. Finally, for 5-FU, we need at least 2 Css samples, and multiple samples during the beginning of the 5-FU infusion to develop a MIPD model.

For irinotecan, SN-38 and SN-38G, a limited sampling strategy is used of two blood samples (2x4ml) at ~2.5h and ~49.5h after start irinotecan infusion that was described in literature to assess AUC_{500h} of irinotecan and SN-38 (53) for cycle 1, cycle 2, and subsequent cycles with 5-FU dose adjustments (≥15%). Using population PK modelling the extra burden of an additional sampling moment can be limited by combining 5-FU and Irinotecan/SN-38 blood sampling. The blood sampling time point is used to determine the systemic drug exposure (AUC) using a population PK modelling. Therefore, with population PK modelling, a concentration at precisely at 49.5 hours is not required to estimate the true Irinotecan/SN-38 exposure (AUC). With the proposed (limited) sampling scheme as defined in this protocol the key population PK parameters can be estimated (volume of distribution and clearance) and therefore an accurate prediction of the AUC's of both 5-FU and Irinotecan can be performed.
As oxaliplatin free fraction is measured exploratory, only one sample in (1x4ml) in cycle 1, cycle 2, and subsequent cycles with 5-FU dose adjustments (≥15%). This chosen time point (2.5h after start infusion oxaliplatin/0.5h after end infusion oxaliplatin) is feasible as free, unbound oxaliplatin has a terminal half-life of only 15-25 minutes (69).

Cycle 1 and 2 are chosen to obtain blood samples to reduce the burden for the patients and no differences in pharmacokinetics are expected between the rest of the cycles. Additionally,

blood samples will be collected in subsequent cycles where dose adjustments of 5-FU are done (≥15%). A limited sampling strategy will be verified throughout the trial to reduce the number of required blood samples where possible.

The 5-FU and its metabolite (5-FUH2) plasma concentrations will be analyzed in pharmacy lab of the AMC, CZE and Isala. The plasma concentration will be analyzed within 10 days after blood sampling, using a validated tandem liquid chromatography-mass spectrometry method (LC-MS/MS).
The irinotecan, SN-38 and SN-38G plasma concentrations will be analyzed in pharmacy lab of the CZE. The plasma concentration will be analyzed retrospectively, using a validated tandem liquid chromatography-mass spectrometry method (LC-MS/MS).
The oxaliplatin free fraction/pUF concentrations will be analyzed retrospectively, using atomic absorption spectrometry on a Thermo Fisher Solaar ICE 3500 graphite-furnace spectrophotometer with Zeeman correction (70).

Dried Blood Spot analysis of 5-FU

PART A only

To assess the reliability of DBS 5-FU measurements as an alternative method to venous plasma sampling measurements, we will use this method at the same sampling times as the plasma determinations during cycles 1 and 2 for DBS validation in a minimum of 40 successfully obtained DBS samples obtained from a total of 25 patients of PART A, according to international guidelines for DBS validation (91). DBS is a finger prick which is a minimal burden for the patient. Four droplets of blood from one finger prick will be collected at t = 2 hours and t = day 3 during cycles 1 and 2.

10.3.7. Toxicity assessment

PART A and PART B

Before the start of subsequent cycles, regular blood sampling will be performed as described before, to investigate the changes in hematologic and non-hematological condition in patients. This is already part of the procedure in standard care. The incidence, severity, and type of AEs and clinical laboratory results will be recorded in HiX/EPIC. Furthermore, toxicity-related hospitalization, delay or discontinuation of chemotherapy will also be recorded. Physicians will score toxicity according to the guidelines from the National Cancer Institute (NCI-CTC AE Version 5.0) (Appendix VII). Severe toxicity is defined as grade ≥ 3. The physician decides whether the patient continues with chemotherapy and the applied dosages when patients develop toxicity.

10.3.8. Efficacy assessments

PART A and PART B

Efficacy of FOLFIRINOX treatment will be expressed in CA 19-9, ORR, DFS, PFS and/or OS. Tumor measurement and response evaluation by CT-scan will be performed according to standard of care practice (~every 3 months), left to the discretion of the treating oncologist. Response will be measured clinically and by CT (classification according to the RECIST criteria 1.1 (71)). Efficacy of FOLFIRINOX in terms of QoL will be determined through questionnaires of PACAP that are

filled in by pancreatic cancer patients partaking in PACAP. With the agreement of the patient, data from filled in PACAP questionnaires of patients will be requested from PACAP.

10.3.9. 5-FU PK Modelling and calculation of 5-FU AUC

PART A and PART B

A population PK model for 5-FU will be developed for the specific population (pancreatic cancer patients treated with FOLFIRINOX) in our centers, based on available 5-FU PK models in literature, historical pharmacokinetic data of around 180 patients with diverse malignancies and performance status (PERFU, FUUT, FLOT and PISA study), and based on all obtained and measured plasma concentrations from study subjects of PART A.

Population pharmacokinetics is the study of pharmacokinetics at the population level, in which data from all individuals in a population are evaluated simultaneously using a nonlinear mixed-effects model. There are five major aspects to developing a population pharmacokinetic model: (i) data, (ii) structural model, (iii) statistical model, (iv) covariate models, and (v) modeling software. Structural models describe the typical concentration time course within the population. Statistical models account for "unexplainable" (random) variability in concentration within the population (e.g., between-subject, between-occasion, residual, etc.). Covariate models explain variability predicted by subject characteristics (covariates). Nonlinear mixed effects modeling software brings data and models together, implementing an estimation method for finding parameters for the structural, statistical, and covariate models that describe the data. A primary goal of most population pharmacokinetic modeling evaluations is finding population pharmacokinetic parameters and sources of variability in a population. Other goals include relating observed concentrations to administered doses through identification of predictive covariates in a target population. Population pharmacokinetics does not require "rich" data (many observations/subject), as required for analysis of single-subject data, nor is there a need for structured sampling time schedules. "Sparse" data (few observations/subject), or a combination, can be used. (92).

Model development will be performed in Nonlinear Mixed Effects Modeling (NONMEM) using patient characteristics and 5-FU plasma concentrations. NONMEM (v7.4.4, Icon Development Solutions, Ellicott City, MD) will be used for modelling 5-FU pharmacokinetics, using PsN toolkit (v5.0.0) (81-83), and Piranã version 2.9.8 (84), as modeling environment. R statistics (v. 3.4.4) will be used for exploratory graphical analysis and for evaluation of the GOF and VPC (85). First order conditional estimation method with interaction (FOCE-I) using posthoc estimation will be used throughout the analysis. The individual derived AUCs, average concentrations and peak concentrations will be correlated with efficacy and toxicity outcomes using logistic regression and/or time to event analysis using the above-mentioned software. The effect potential covariates (e.g. demographic, disease stage and pharmacogenetic (*DPYD)*) on 5-FU pharmacokinetics will be investigated using stepwise covariate modelling (SCM) function implemented with Perl-Speaks-NONMEM[12]. Both a forward inclusion ($p < 0.05$) and a backward elimination process ($p < 0.01$) will be performed. The effects of continuous covariates will be investigated with both linear regression and power regression, and also allometric for bodyweight. Simulations in the NONMEM software (Version 6, Globomax LLC, Hanover, MD, USA) will be performed to generate MIPD algorithms of 5-FU. The 5-FU Pop-PK/MIPD model that best fits the PART A data will be selected. The developed 5-FU Pop-PK model and MIPD

algorithm will be implemented in CE-software InsightRx Nova (Version 1.43.3, San Francisco, USA) for individual population PK modelling of 5-FU and MIPD of 5-FU in PART B subjects.
The developed 5-FU Pop-Pk model is used to calculate the individual PK parameters and to calculate AUCs.

10.3.10. 5-FU Dose advice – 5-FU MIPD

PART B only

With the developed 5-FU population-PK model available in InsightRX and the individual patient characteristics, the initial 5-FU starting dose (cycle 1) will be determined for each patient (MIPD). Thereafter (cycles 2+), the measured $AUC_{0\text{-}46h}$ of 5-FU will be used to calculate the adequate 5-FU dose in the next cycle with the 5-FU Pop-PK/MIPD model within InsightRX Nova. The model will be used to calculate the individual PK parameters and to calculate AUCs reached at each dose level based on relevant covariates and measured 5-FU plasma concentrations. The AUC target range of 5-FU is $AUC_{0\text{-}46h}$ 20-30 mg*h/, to which the dosages of 5-FU will be adjusted in PART B, while taking into account the individual's toxicity profile at each cycle. However, we will use maximum dose adjustments to ensure patient safety. The safety framework for dose adjustment based on $AUC_{0\text{-}46h}$ of 5-FU can be found in Table 8. It consists of a maximum of 130% dose intensity (*DPYD* wildtypes) and maximum dose escalations of 20% in absolute dose intensity per cycle (*DPYD* wildtypes*)*. In *DPYD* variant carriers, lower percentages (table 8) are to be used because these groups are generally more at risk for 5-FU toxicity. For cycle 1, initial dose is calculated by the MIPD algorithm and based solemnly on patient characteristics. Then, based on clinical tolerability and measured 5-FU AUC, the 5-FU dose in subsequent cycles will be further individualized (i.e. reduced, maintained, or decreased), in order to optimize the dose for the individual patient. Doses of other concomitant anticancer drugs will be left unchanged. A suggested decision tree has been designed that can be used as an additional tool in PART B by treating physicians for 5-FU dosing decisions, which takes into account both 5-FU $AUC_{0\text{-}46h}$ (determined by 5-FU Pop-PK/MIPD model) and toxicity profile (See APPENDIX VIII). Use of the decision tree is at the discretion of the treating physician.

Table 8: Framework for model-informed precision dosing of 5-FU in PART B. Dose intensities (%) are calculated in relation to standard BSA-base dosages in mg/m².

5-FU target AUC (mg*h/L) (anticipated)	$AUC_{0\text{-}46h}$ 20 – 30 mg*h/L
5-FU dose at 100% dose intensity	Classic FOLFIRINOX Bolus 400 mg/m² + continuous infusion 2400 mg/m²
	mFOLFIRINOX Continuous infusion 2400 mg/m²
Recommended change in 5-FU dose to reach $AUC_{0\text{-}46h}$ 20-30 mg*h/L for next treatment cycle	Calculated for each patient with 5-FU Pop-PK/MIPD model →dependent on patient characteristics
Maximum 5-FU dose intensity (%) cycle 1	*DPYD* wildtype: 120%

	DPYD gene activity score 1.5: 75%
	DPYD gene activity score 1.0: 50%
Maximum 5-FU dose intensity (%) cycle 2+	*DPYD* wildtype: 130%
	DPYD gene activity score 1.5: 100%
	DPYD gene activity score 1.0: 60%
Maximum 5-FU dose escalation per cycle in <u>absolute</u> dose intensity %	*DPYD* wildtype: 20%
	DPYD gene activity score 1.5: 15%
	DPYD gene activity score 1.0: 10%

10.3.11. Additional assessments for sub-analyses

PART A and PART B

<u>Body composition</u>

To investigate the association between body composition and the exposure of chemotherapeutic agents, skeletal muscle mass, visceral adipose tissue mass, subcutaneous adipose tissue mas, as well as the radiation attenuation of these tissue compartments will be analyzed for their correlation with circulating levels of 5-FU and its metabolites. Furthermore, the association between these body composition features and 5-FU-related toxicity will be investigated. Available routine diagnostic abdominal CT-scans will be analyzed by Mosamatic (Maastricht University).

<u>Circulating tumor DNA</u>

An additional blood sample (1x10ml EDTA plasma (or streck tube)) at baseline and at standard follow-up CT scan moments will be taken to assess potential circulating tumor cells/markers present in whole blood. Circulating tumor markers may be used for association analyses with 5-FU, irinotecan/SN-38 AUC to e.g. investigate the influence of drug exposure on treatment resistance/sensitivity. Samples will be sequenced using a tumor-focused Oncomine Pan-Cancer Cell-Free Assay (NGS) (91).

<u>PGx analysis</u>

As part of standard care, germline DNA will be isolated from human whole blood for *UGT1A1* and *DPYD* genotype analysis. Leftover germline DNA will be retrospectively used for additional PGx analysis measured through real-time PCR for identification and/or validation of relevant allele variations that are associated with FOLFIRINOX treatment outcomes (including pharmacokinetics, toxicity and efficacy of treatment).

<u>Microbiome analysis</u>

One fecal sample will be collected prior to the first FOLFIRINOX cycle. If this moment is unfeasible for the patient, one fecal sample will be collected during the first FOLFIRINOX cycle instead. In these fecal samples, the B-glucuronidase activity will be measured. One sample per patient is sufficient to correlate the β-glucuronidase activity to the occurrence of toxicity. Fecal samples will be collected at home by the patients themselves, using a patient-friendly, easy-to-use collection kit. Patients are asked to fill two tubes at one timepoint. Cooled transporter container (Sarstedt, Nümbrecht, Germany) will be provided to the patients to ensure that the

samples remain frozen during the transport to the hospital. Fecal samples will be stored in the local center until analysis.

10.3.12. Safety assessments

PART A and PART B

Also described above under "10.3.6. Toxicity assessments". Before each chemotherapy cycle, standard-of-care blood sampling will be performed to assess the changes in hematologic and non-hematological condition in patients. As standard-of-care, each patient is seen by their treating physician before each new chemotherapy cycle to assess adverse events, vital signs, physical examination and laboratory assessments. The incidence, severity, and type of AEs and clinical laboratory results will be recorded in HiX/EPIC. Furthermore, if needed, dose modification, delay or discontinuation of chemotherapy will be done and recorded in HiX/EPIC. Physicians will score toxicity according to the guidelines from the National Cancer Institute (NCI-CTC AE Version 5.0) (Appendix VII). Severe toxicity is defined as grade ≥ 3. The physician decides whether the patient continues with each new cycle of chemotherapy and the applied dosages when patients developed toxicity as per standard of care. In case of toxicity, patients can be treated with standard supportive care until the toxicity has been diminished.
See also Chapter 11.

11. SAFETY REPORTING

Since 5-FU is a registered drug for several decades and treatment as described will be applied for the registered indications, only new and/or unexpected adverse events will be reported to the METC. In PART A, study treatment with 5-FU is according to international guidelines and local standardized treatment protocols and conform the SPC, no changes are made in the treatment regimen. Therefore, the report of AEs, SAEs or SUSARs of 5-FU to the METC within PART A is not deemed applicable.
For irinotecan and oxaliplatin, the study treatment is according to international guidelines and local standardized treatment protocols and conform the SPC, no changes are made in the treatment of irinotecan and oxaliplatin. Therefore, the report of AEs, SAEs or SUSARs to the METC for irinotecan and oxaliplatin is not deemed applicable.

11.1.1. Adverse events (AEs)

Adverse events are defined as any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment.

11.1.2. Serious adverse events (SAEs)

Serious adverse event is any untoward medical occurrence in a patient or trial subject that at any dose:

- results in death,
- is life-threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect

An elective hospital admission will not be considered as a serious adverse event.

11.1.3. Suspected unexpected serious adverse reactions (SUSARs)

Unexpected adverse reactions are SUSARs if the following three conditions are met:

1. The event must be serious;
2. There must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;
3. The adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in the reference safety information (RSI). See 5-FU SPC for RSI.

11.2. Recording of AEs/SAEs/SUSARS

Adverse events are defined as any undesirable experience occurring to a patient during the study, whether or not considered related to the drug. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory or vital sign finding), symptom, or disease temporally associated with the study participation. All adverse events reported spontaneously by the patients or observed by the physician and his staff will be recorded in HiX/EPIC and the eCRF.

The intensity of clinical AEs is graded based on the NCI-CTCAE v5.0 criteria (APPENDIX VII):

- Grade 1: mild
- Grade 2: moderate
- Grade 3: severe
- Grade 4: life-threatening
- Grade 4: death

For each AE the relationship to 5-FU, irinotecan and oxaliplatin as judged by the investigator:

- Definitely;
- Probable;
- Possible;
- Unlikely;
- Unrelated.

The chronicity of the AE will be classified by the investigator on a three-item scale as defined below:

- Single occasion: single event with limited duration;
- Intermittent: several episodes of an event, each of limited duration;
- Persistent: event which remained indefinitely.

Eventual actions taken will be recorded.

11.3. Reporting of AEs and SAEs

11.3.1. Reporting of SAEs by the investigator and sponsor

SAEs and SUSAR's will be reported according to the following procedure:

The investigator will document AEs in source documents and in the eCRF and report the SAEs and SUSAR's to the sponsor according to the CTCAE (v5.0) (APPENDIX VII). SAEs/SUSARs will be reported to the sponsor within 24 hours of obtaining knowledge of the event, with the exception of 11.5.3.

11.3.2. List of SAEs which do not require immediate reporting and procedure for reporting

In PART A of this study, treatment with FOLFIRINOX is according to international guidelines and local standardized treatment protocols and conform the SPC, no changes are made in the treatment regimen. Therefore, the report of AEs, SAEs or SUSARs to the METC within PART A (pharmacokinetic study) of PERFUPANC is not deemed applicable. In PART A, only serious adverse events related to the study procedures, e.g. extra venapunctures for pharmacokinetic analysis, will be regarded as serious adverse events.

In PART B, dose escalations for 5-FU may be applied because of MIPD of 5-FU. 5-FU dose escalations could lead to increased 5-FU toxicity. However, treatment with 5-FU is a registered therapy for pancreatic cancer and there is sufficient experience with treatment of toxicity of 5-FU, and serious 5-FU (grade ≥ 3) toxicity is common in patients treated with 5-FU. Therefore, 5-FU-related serious toxicities may be considered SAEs, but not all 5-FU-related SAEs require immediate reporting to the sponsors.

SAEs that do not require immediate reporting are:

- SAEs in PART A of the study
- SAEs in PART B patients that received standard-of-care 5-FU dosages (no dose escalations performed)
- SAEs unrelated or unlikely related to 5-FU
- NCI-CTCAE (v5.0) grade ≤3 SAEs

SAEs that do require immediate reporting are:

- NCI-CTCAE (v5.0) grade 4 or 5 toxicity in patients that received 5-FU dose escalations in PART B of the study
- SAEs that result in persistent or significant disability/incapacity

For irinotecan and oxaliplatin, the study treatment is according to international guidelines and local standardized treatment protocols and conform the SPC, no changes are made in the treatment of irinotecan and oxaliplatin. Therefore, immediate reporting of SAEs of irinotecan and oxaliplatin is not deemed applicable.

11.4. Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs need to be reported till end of study within the Netherlands, as defined in the protocol. The end of the study is defined as the last patient's last received FOLFIRINOX treatment cycle.

11.5. Reporting of SUSARs by the sponsor to EudraVigilance

The sponsor will keep detailed records of all AEs which are reported to him/her by the investigator or investigators.

The sponsor will report electronically and without delay to EudraVigilance all relevant information about any SUSAR.

The period for the reporting of SUSARs by the sponsor to EudraVigilance will take account of the seriousness of the reaction and will be as follows:

- In the case of fatal or life-threatening SUSARs, as soon as possible and in any event not later than **7 days** after the sponsor became aware of the reaction;
- In the case of non-fatal or non-life-threatening SUSARs, not later than **15 days** after the sponsor became aware of the reaction;
- In the case of a SUSARs which was initially considered to be non-fatal or nonlife threatening but which turns out to be fatal or life-threatening, as soon as possible and in any event not later than **7 days** after the sponsor became aware of the reaction being fatal or life-threatening.

Where necessary to ensure timely reporting, the sponsor may, in accordance with section 2.4 of Annex III, submit an initial incomplete report followed up by a complete report.

11.6. Annual safety report

Regarding investigational medicinal product 5-FU, the sponsor shall submit annually through CTIS to all Member States concerned a report on the safety of 5-FU MIPD.
This is only applicable for 5-FU in PART B, as 5-FU is an authorized IMP that is used since more than 20 years and is used as registered in PART A.

11.7. Unblinding procedures for safety reporting

Not applicable.

11.8. Temporary halt for reasons of subject safety

The sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will submit the notification through CTIS without undue delay of a temporary halt but not later than in 15 days of the date of the temporary halt. It shall include the reasons for such action and specify follow-up measures. The study will be suspended pending a further positive decision by the concerned member state. The investigator will take care that all subjects are kept informed.

11.9. Urgent safety measures and other relevant safety reporting

Where an unexpected event is likely to seriously affect the benefit-risk balance, the sponsor and the investigator will take appropriate urgent safety measures to protect the subjects. In addition the sponsor will notify the Member States concerned, through CTIS, of the event and the measures taken. That notification will be made without undue delay but no later than **7 days** from the date the measures have been taken.

11.10. Data Safety Monitoring Board (DSMB)/Data Monitoring Committee (DMC)

A DSMB will receive and review the progress and accruing data of this trial and provide advice on the conduct of the trial to the Trial Steering Committee. The reason for a DSMB in this study in specific is to:

1. Assess whether PART B may be initiated after completion of PART A.
2. Monitor the safety of 5-FU MIPD performed in PART B of this study.

The DSMB will meet:

- Before start of inclusion;
- Shortly after the first 30 patients in PART A have been included to receive an update from the steering committee about study progress;
- After completion of the first cohort (PART A, n=50), but before start of PART B.
- After the first 30 included patients in PART B have completed their first two cycles of FOLFIRINOX treatment;
- At study end.

Details meeting moment after completion of first cohort (PART A, n=50):

The DSMB will evaluate if PART A has been completed and whether PART B may be initiated based on the results from PART A. The AUC target range of 20-30 mg*h/L for 5-FU will be validated for the pancreatic cancer patients undergoing FOLFIRINOX in PART A and a 5-FU Pop-PK/MIPD model will be developed from the PART A dataset. For this, the DSMB will receive and review the (analyzed) dataset from PART A (including the established 5-FU Pop-PK/MIPD model).

Criteria to proceed with PART B:

- Completion of PART A
- A developed Pop-PK FU/MIPD model implemented in Insight RX Nova as a tool for 5-FU dosing recommendations
- The population distribution of 5-FU $AUC_{0\text{-}46h}$ PART A subjects being more or less in line with the population distribution described in literature (see also section 12.1 of study protocol).
- The proportion of PART A patients being outside 5-FU $AUC_{0\text{-}46h}$ target range 20-30 mg*h/L (when dosed on BSA), is ≥10% of patients.

The DSMB may therefore have input into the protocol of PERFUPANC PART B.

Details meeting moment during second cohort (PART B, n=30):

The DSMB will assess the safety of PART B (MIPD of 5-FU) after n=30 patients have been included in PART B. For this, the DSMB will receive a safety/toxicity report of PART B included patients and a safety/toxicity report of PART A included patients for comparison.

The DSMB will report its recommendations in writing to the Trial Steering Committee or sponsor's representative. Possible recommendations from the DSMB could include:

- No action needed, trial continues as planned
- Early stopping due, for example, to clear benefit or harm of a treatment, futility, or external evidence
- Stopping recruitment within a subgroup
- Extending recruitment or extending follow-up
- Sanctioning and/or proposing protocol changes

The DSMB is composed of members independent of the current study, that have demonstrable expertise in oncology and pharmacology/therapeutic drug monitoring, in order to perform adequate safety and quality analyses.

Composition of the independent DSMB committee:

- Dr. Jan Beumer, Jan Hendrik Beumer, PharmD, PhD, DABT.
  Professor of Pharmaceutical Sciences and Medicine, An NCI-designated Comprehensive Cancer Center, affiliated with the University of Pittsburgh School of Medicine.
- Dr. Frans Opdam, MD, PharmD, PhD
  Medical Oncologist-Clinical Pharmacologist at NCI-AVL

- Independent epidemiologist-statistician at Catharina Hospital Eindhoven: Dr. Marcel van 't Veer, PhD

See DSMB charter for more details.

Monitoring according to ICH GCP will be performed by the Clinical Research Associate of the Catharina Hospital Eindhoven or the person to whom the monitoring tasks have been delegated.
Amongst others the following will be reviewed:

- Compliance with the protocol, ICH_GCP and all applicable regulatory requirements.
- Consent procedures, including date of consent and signatures
- Study progress
- Completion of the (e)CRFs and verification of data against the source data
- Storage, dispensing and accountability of study medication.

12. STATISTICAL ANALYSIS

12.1 Planned analysis

A change to the data analysis methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Any retrospective or exploratory analyses not defined by the protocol or the statistical analysis plan will be explained in the clinical study report.

12.1.1 General

The current study is composed of two parts: PART A and PART B. Using collected data from the PART A cohort, a 5-FU Pop-PK model will be developed and applied in the PART B cohort for MIPD of 5-FU. The 5-FU AUCs of patients dosed with BSA will be calculated with the 5-FU Pop-PK model to determine the 5-FU $AUC_{0\text{-}46h}$ population distribution and to verify how this relates to the recommended 5-FU AUC target range (20-30 mg*h/L). In PART B, the 5-FU AUCs of patients dosed with the 5-FU Pop-PK/MIPD model and the 5-FU AUCs are calculated with the model to determine the 5-FU $AUC_{0\text{-}46h}$ distribution and to verify how this relates to the recommended 5-FU AUC target range (20-30 mg*h/L). For the primary endpoint, the percentage of patients that reaches 5-FU AUC target range within two FOLFIRINOX cycles will be compared between the PART A cohort and PART B cohort. The hypothesis is that MIPD of 5-FU will lead to a higher percentage of patients reaching 5-FU AUC target range compared to the percentage of patients from PART A treated with standard (BSA) dosed 5-FU.

Patient demographics, characteristics, toxicity, plasma concentrations and endogenous biomarker concentrations at each time point of measurement will be described by descriptive statistics. 5-FU AUC will be described as a continuous variable, as well as a qualitative variable categorized in three groups (below, within and above target range) or in two groups (target range reached or not). In this study, severe toxicity is defined as CTCAE grade ≥ 3 toxicity. Data will be tested for normal distribution assessing skewness and kurtosis and by performing normality test (Kolmogorov-Smirnov-test). All binary and categorical variables are expressed as n (%), and continuous variables as mean (standard deviation), or median [range], depending on distribution. 95% confidence intervals will be calculated and presented, where appropriate. Associations with dichotomous outcomes will be analysed using Chi square tests or Fisher's exact test, where appropriate. Continuous variables, such as pharmacokinetic parameters will be analysed using student's t-test. In case of non-normality in the data the nonparametric Mann-Whitney U test or Wilcoxon rank test will be used. Results of regression analyses are reported as odds ratios with 95% confidence intervals. Statistical analyses with *p*-values of $p < 0.05$ will be considered statistically significant. Statistical analyses will be performed with SPSS software (IBM SPSS Statistics 24) and R statistics (v. 3.4.4.).

Missing data will be tracked in Research Manager EDC. Missing data will be identified using summary methods. Descriptive statistics and/or statistical tests (e.g. t-tests, ANOVA, chi-square, correlation) will be used to compare the characteristics of complete and incomplete cases, to quantify the impact of missing on the dataset, to identify the type of missing data, and the patterns of missingness. Missing data are marked as missing completely at random (MCAR), missing at random (MAR) or not missing at random (NMAR). When missing data depends on some of the observed variables, but the values that are missing are random, data is marked as MAR. When the pattern of missing data is related to other variables in the dataset and probability of the missing data depends on the missing values themselves, the data will be marked as NMAR. All other missing data (non-explainable/no missingness pattern) will be marked as MCAR. When data is MCAR, analyses will be undertaken using only observations that have complete data. For MAR cases, missing data will be either imputed or analyses will be undertaken

using only observations that have complete data, where appropriate. In the case of NMAR cases, the NMAR data and its size and impact on the dataset will be further analyzed, and the handling will be discussed with a statistician. A complete case analysis will be performed for the primary endpoint.

12.1.2 5-FU Population PK model development for applying MIPD of 5-FU

See also Methods section 10.3.9

PART A

A population PK model for 5-FU will be developed for the specific population (pancreatic cancer patients treated with FOLFIRINOX) in our centers, based on available 5-FU PK models in literature , historical pharmacokinetic data of around 180 patients with diverse malignancies and performance status (PERFU, FUUT, FLOT and PISA study), and based on all obtained and measured plasma concentrations from study subjects of PART A.

Model development will be performed in Nonlinear Mixed Effects Modeling (NONMEM) using patient characteristics and 5-FU plasma concentrations. NONMEM (v7.4.4, Icon Development Solutions, Ellicott City, MD) will be used for modelling 5-FU pharmacokinetics, using PsN toolkit (v5.0.0) (81-83), and Piranã version 2.9.8 (84), as modeling environment. R statistics (v. 3.4.4) will be used for exploratory graphical analysis and for evaluation of the GOF and VPC (85). First order conditional estimation method with interaction (FOCE-I) using posthoc estimation will be used throughout the analysis. The effect of potential covariates (e.g. demographic, disease stage, and pharmacogenetic (*DPYD*)) on 5-FU pharmacokinetics will be investigated using stepwise covariate modelling (SCM) function implemented with Perl-Speaks-NONMEM[12]. Both a forward inclusion ($p < 0.05$) and a backward elimination process ($p < 0.01$) will be performed. The effects of continuous covariates will be investigated with both linear regression and power regression, and also allometric for bodyweight. Simulations in the NONMEM software (Version 6, Globomax LLC, Hanover, MD, USA) will be performed to generate MIPD algorithms of 5-FU. The 5-FU Pop-PK/MIPD model that best fits the PART A data will be selected. The developed 5-FU Pop-PK model and MIPD algorithm will be implemented in CE-software InsightRX Nova (Version 1.43.3, San Francisco, USA) for individual population PK modelling of 5-FU and MIPD of 5-FU in PART B subjects. The model will be used to calculate the individual PK parameters and to calculate AUCs reached at each dose level based on relevant covariates and measured 5-FU plasma concentrations.

PART B

At the end of PART B, the 5-FU population PK/MIPD model will be updated based on all obtained and measured plasma concentrations from PART B patients as well.

12.1.3 Primary endpoint analysis: *percentage of patients achieving 5-FU AUC target range*

PART A*: percentage of patients achieving 5-FU AUC target range when dosed on BSA*

The distribution 5-FU AUC_{046h} of patients treated with BSA-dosed 5-FU (PART A) and the percentage of PART A patients that achieve therapeutic (AUC) range of 5-FU within two cycles will be depicted descriptively.

The $AUC_{0\text{-}46h}$ target range of 5-FU between 20 and 30 mg*h/L, is validated by determining whether the proportion of PART A patients with an AUC_{046h} below, within and above 20 and 30 mg*h/L is similar to the population distribution of 5-FU $AUC_{0\text{-}46h}$ described for previously other real-world

populations treated with 5-FU (Beumer et al. 2019 and Li et al. 2023) (descriptive statistics). A proportion of ≥10% PART A patients being outside 5-FU $AUC_{0\text{-}46h}$ target range 20-30 mg*h/L (when dosed on BSA) is considered an indication for applying MIPD of 5-FU in our pancreatic cancer population. Lastly, the relative standard deviation (RSD) of 5-FU AUCs of PART A patients is calculated, primarily for cycles 1 and 2 of treatment. A RSD of ≥ 20% in 5-FU $AUC_{0\text{-}46h}$ of PART A patients indicates a large inter-patient variability and would further support application of MIPD of 5-FU.

PART B: *percentage of patients achieving 5-FU AUC target range when dosed with MIPD model*
The distribution 5-FU AUC_{046h} of patients treated with MIPD of 5-FU (PART B) and the percentage of PART B patients that achieve therapeutic (AUC) range of 5-FU within two cycles will be depicted descriptively. Treatment delay due to the MIPD process will be depicted descriptively.
For PART B, the primary endpoint (percentage of patients achieving 5-FU $AUC_{0\text{-}46h}$ target range (20-30 mg*h/L)) primarily determines the success of MIPD of 5-FU. PART A patients will be defined as the control group and PART B patients will be defined as the intervention group.

MIPD of 5-FU will be considered successful (safe and feasible) only if:

- The number of patients in the intervention group (PART B) that achieve 5-FU AUC target range within two cycles is higher than the number of patients in the control group (PART A) that achieve 5-FU AUC target range within two cycles. Data will be presented as n (%) and compared between the control and intervention group using Chi-square test or Fisher's exact test, where appropriate. No adjustment for multiple testing will be applied for the primary endpoint.

12.1.4. Secondary endpoint analyses

Secondary objectives and related endpoints are mainly descriptive in nature and to gain preliminary insights. When there is an overall difference between the groups, we will perform post-hoc analyses to further explore these results. Correction for multiple testing, for instance by Bonferroni correction, is taken into account where appropriate.

Pharmacokinetic analyses

PART A and PART B: *Pharmacokinetics of 5-FU, Irinotecan and Oxaliplatin*
Plasma concentrations at each time point of measurement will be presented. Population (Pop) pharmacokinetic (PK) parameters (clearance (Cl), volume of distribution (Vd), Css, Cmax, AUC) of 5-FU, Irinotecan, Oxaliplatin and its relevant metabolites will be estimated/calculated based on measured plasma concentrations, and are descriptive in nature.
To take into account repeated measurements analysis of PK parameters (plasma concentrations at multiple time points and for multiple treatment cycles), repeated measurements will be summarized (e.g. mean, change, most important value,…) to obtain a single outcome for analysis on derived summaries, where appropriate.
Determining the intra-individual variation in 5-FU, Irinotecan, SN-38 and Oxaliplatin exposure between the different cycles will be assessed by repeated measure analysis. Also, determining

the inter-individual variation in 5-FU, Irinotecan, SN-38 and Oxaliplatin exposure, plasma concentrations of 5-FU will be assessed by repeated measure analysis.
Maximum A Posterior Bayesian Estimation (MAPBE) will be performed in NONMEM to get insights in the best limit sampling strategy.
Pearson correlation test will be used to measure the strength of linear association between 5-FU exposure and *DPYD* gene activity and biomarker plasma concentration ratios DHU/U and DHU/T. Irinotecan/SN-38 exposure across different *UGT1A1* genotypes and 5-FU exposure across different *DPYD* genotypes will be presented descriptively.

Toxicity/safety analyses

PART B: *To determine the safety of MIPD of 5-FU*

It is further evaluated in PART B whether 5-FU dose modifications based on MIPD of 5-FU are safe, or whether they can be increased on need to be increased. MIPD of 5-FU will be considered safe if:

- The incidence of severe toxicity (secondary endpoint) is on average ≤20% higher (relative) for the intervention group (PART B) compared to the control group (PART A). Incidence of severe toxicity may additionally be compared between the control and intervention group using Chi-square test of Fisher's exact test, where appropriate. These tests may be considered as indicative for the potential differences in the results and no adjustment for multiple testing will be applied for this secondary endpoint.

AND:

- The incidence of severe toxicity in intervention group subjects (PART B) that received 5-FU dose escalation based on MIPD is ≤16.67% (descriptive statistics). The maximum of 16.67% is based on the standard 3+3 study design for dose-finding phase-I studies, where a maximum of 1/6 patients experiencing a severe adverse event (Dose Limiting Toxicity) upon dose escalation is accepted.

PART A and PART B: *To get insights in the optimal therapeutic exposure (AUC) of 5-FU, Irinotecan and Oxaliplatin*

The individual derived AUCs and/or plasma concentrations of 5-FU, Irinotecan, SN-38 and Oxaliplatin will be correlated with toxicity outcomes using logistic regression. Fisher's exact test or $\chi 2$ test will be used to analyze the frequency of AEs and severe toxicity below, within and above the 5-FU target range.

Feasibility analyses

PART B: *To determine the feasibility of MIPD of 5-FU*

Turn-around-time of 5-FU MIPD and incidence of treatment delay due to MIPD of 5-FU will be depicted descriptively.

- For feasibility of MIPD of 5-FU, there has to be no logistic treatment delay due to the MIPD process (descriptive).

To get further insight in the feasibility of MIPD of 5-FU in routine clinical practice, compliance of treating physicians to 5-FU dosing advice based on MIPD will be described descriptively:

- Compliance to 5-FU MIPD dosing advice by treating physicians will be expressed as n (%), and identified reasons for (no) compliance will be described.

Efficacy analyses

PART B: *To get insights in the preliminary clinical benefit of MIPD of 5-FU*

Long-term efficacy outcomes (disease-free survival (DFS), progression-free survival (PFS) and overall survival (OS)) will be compared between control group (PART A) and intervention group (PART B) using time-to-event analysis (Kaplan-Meier survival analysis by a log-rank test and Cox regression). Results will be indicative for the impact of MIPD of 5-FU on treatment efficacy. A subgroup analysis will be undertaken for this endpoint analysis; (neo)adjuvant vs. palliative setting.

PART A and PART B: *To get insights in the optimal therapeutic exposure (AUC) of 5-FU, Irinotecan and Oxaliplatin*

The individual derived AUCs and/or plasma concentrations of 5-FU, Irinotecan, SN-38 and Oxaliplatin will be correlated with long-term efficacy outcomes (DFS, PFS, OS) and using time-to-event analysis. DFS, PFS and OS will be analyzed for different subgroups (e.g. below, within and above 5-FU target range) with Kaplan-Meier survival analysis by a log-rank test and Cox regression. A subgroup analysis will be undertaken for this endpoint analysis; (neo)adjuvant vs. palliative setting.

Covariate analyses

PART A and PART B: *To get insights in patient-and treatment characteristics associated with 5-FU and Irinotecan exposure and treatment-related toxicity*

Nonlinear Mixed Effects Modeling (NONMEM) will be used for assessing the effect of covariates on 5-FU exposure/pharmacokinetics, as described under 12.1.2. In the same way, the effect of covariates on Irinotecan/SN-38 exposure/pharmacokinetics will be explored. The effects of covariates (patient- and treatment characteristics) on toxicity outcomes will also be investigated by univariable and multivariable regression analyses.

Exploratory analyses

Exploratory objectives and related endpoints in the current study are generally explorative in nature and hypothesis generating. They will mostly involve descriptive statistics. Correction for multiple testing, for instance by Bonferroni correction, is taken into account where appropriate. Exploratory analysis after study end will be analyzed in a separate report(s) from the other primary and secondary study endpoints.

PART A and PART B

- For the clinical validation of 5-FU Dried Blood Spot: validation/analyses are done in accordance with the international guideline for DBS validation (91). In short, the RSD (%) will be calculated to determine the variation in measured 5-FU concentrations between dried blood spots. The reliability of 5-FU DBS measurements will be assessed by comparing 5-FU DBS measurements and 5-FU venous plasma sample measurements. For this, regression analyses (Passing-Bablok or weighted Deming regression) will be performed to measure the correlation, followed by an agreement and bias estimation test (Bland Altman difference plot).
- The genotyping/PGx analysis will test multiple comparisons / genotypes with treatment outcome to identify and/or validate possible relevant variants/mutations. The Bonferroni correction will be applied for correction for multiple testing.
- The exploratory ctDNA analyses will describe the (amount of) measured ctDNA found in human whole blood in pancreatic cancer patients, to give insights in the tumor response (sensitivity/resistance) to FOLFIRINOX treatment in pancreatic cancer patients.
- The microbiome analysis will assess the association between the activity of the gut microbiota-derived enzyme β-glucuronidase will be associated with increased gastrointestinal toxicity and decreased QoL and OS, using univariate and multivariable regression. The Pearson correlation test will be used to measure the strength of linear association between irinotecan/SN-38 exposure and the activity of enzyme β-glucuronidase.
- The body composition analysis will assess the association between body composition features (skeletal muscle mass, visceral adipose tissue mass, subcutaneous adipose tissue mass and radiation attenuation of these tissue compartments) and toxicity outcomes using univariate and multivariable regression analysis. The Pearson correlation test will be used to measure the strength of linear association between 5-FU, Irinotecan/SN-38 and oxaliplatin exposure and different body composition features.

12.2 Sample size, trail power and level of significance used

The primary objective of this observational study is to determine the percentage of patients achieving optimal 5-FU exposure as previously defined. With the knowledge of the 5-FU pharmacokinetics from the ongoing PERFU study in Amsterdam UMC and Combigapp study in Isala Hospital, and the expected subgroups in this study (e.g. irinotecan and oxaliplatin exposure, *UGT1A1* and *DPYD* genotype, treatment regimen, and other covariables), it is expected that 50 patients will be sufficient to answer our primary objective. Moreover, it is possible to generate a population PK model using NONMEM statistics with 50 patients. Based on previous studies,[20,24] we expect 22% of patients to be within 5-FU AUC target range when dosed on BSA (PART A) and that we can increase this to 50% of patients in PART B by dosing based on 5-FU MIPD. We will compare the PART A and PART B cohort to test this hypothesis and the level of statistical significance is set at $p < 0.05$, and a power of 80% is chosen. Based on this information, PS version 3.1.2. was used to calculate a total of 45 control (PART A) and 45 experimental (PART B) subjects to be able to reject the null hypothesis that the percentage of patients within 5-FU AUC target range for BSA-dosed and MIPD-dosed patients is equal. Taking into account possible drop-out, incomplete data, and loss-to-follow-up, we will include a total of 100 patients (50 for PART A and 50 for PART B).

13. ETHICAL CONSIDERATIONS

13.1. Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (Fortaleza October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO), and other appropriate guidelines, regulations and acts.

13.2. Recruitment and informed consent procedures

The investigator must fully explain the trial to the patient. The investigator is responsible to obtain written informed consent from each patients participating in this clinical trial. The patients will receive written information about the aims, methods, objectives and potential hazards of the study. Furthermore, procedures that are part of standard care and procedures in this trial will be explained. The investigator must also explain to patients that they can withdraw the study at any time for any reason if they wish to do so without any consequences. Potential participants will be attended about the existence of the study by their treating physician (oncologist) and will be given the patient information / informed consent form on paper by their treating physician (oncologist). A study investigator will contact the potential study participant to further explain the study and answer the potential participant's questions. Patients have at least 7 days to consider their decision. The patients will be asked to give informed consent when they want to participate in this study by signing and dating an informed consent form. If a patient is unable to read, write or comprehend verbal information, and thus is unable be informed about the current study, the patient will not be included in the current study. Written informed consent signed by the participant and investigator will be obtained before any study procedures are performed. Procedures that are part of standard care and are not intended for study-specific purposes for this study, may occur before informed consent is obtained. The original of the informed consent form will be filed according to local practices in the study file or patient file. A copy will be given to the patient.

13.3. Benefits and risks assessment, group relatedness

Not applicable since minors or incapacitates subjects are not eligible for the study.

13.4. Compensation for injury

The Catharina Hospital has taken out the compulsory insurance, in accordance with legal requirements in the Netherlands (Article 7 WMO and the Measure regarding Compulsory Insurance for Clinical Research in Humans of July, 2015). This insurance provides cover for damage to research subjects through injury or death caused by the study:

- €650.000,- for death or injury for each subject who participates in the research;
- €5.000.000,- for death or injury for all subjects who participate in the research;
- €7.500.000, - for the total damage incurred by the organisation for all damage disclosed by scientific research for the Catharina hospital as ''Sponsor'' in the meaning of said Act in each year of insurance coverage.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

13.5. Compensation for subjects

Enrolled patients do not receive any incentives or compensation through participation in this study.

13.6. Compensation for investigators

Investigators do not receive any incentives or compensation through participation in this study.

14. ADMINISTRATIVE ASPECTS, MONITORING AND CONFIDENTIALITY

The study will be conducted in compliance with the protocol, with Clinical Trials Regulation No 536/2014, with Medical Device Regulation (EU) 201/745 and with the principles of good clinical practice (ICH-GCP).

14.1. Approval initial application and substantial modifications

The trial protocol, informed consent form, subject information leaflet, investigational medicinal product dossier, investigators brochure and any other documents required by the Regulation will be submitted for the regulatory approval before the clinical trial is started via CTIS .

The sponsor will also submit and obtain approval for substantial modifications to the original approved documents via CTIS.

A 'substantial modification' is defined in the CTR as any change to any aspect of the clinical trial which is made after notification of a decision referred to in Articles 8, 14, 19, 20 or 23 and which is likely to have a substantial impact on the safety or rights of the subjects or on the reliability and robustness of the data generated in the clinical trial.

Amendments are changes made to the study protocol after a favorable opinion by the accredited METC has been given. A 'substantial amendment' is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be submitted to the METC that gave a favorable opinion and via CTIS. Non-substantial amendments will not be notified to the accredited METC and CTIS, but will be recorded and filed by the study coordinator.

14.2. Monitoring

Monitoring according to ICH GCP will be performed by the Clinical Research Associate of the Catharina Hospital Eindhoven or the person to whom the monitoring tasks have been delegated. Amongst others the following will be reviewed:

- Compliance with the protocol, ICH_GCP and all applicable regulatory requirements.
- Consent procedures, including date of consent and signatures
- Study progress
- (Serious) Adverse Events
- Completion of the (e)CRFs and verification of data against the source data
- Storage, dispensing and accountability of study medication.

14.3. Recording, handling and storage of information

14.3.1. Handling of data and data protection

Data will be collected and processed in accordance with the General Data Protection Regulation (EU) 2016/679. All patient material will be coded and handled confidentially. The study coordinators will retain the originals of all source documents generated at the participating study sites for a period of at least 25 years after study completion. All records identifying the patients will be kept confidential and will not be made publicly available. Study results will be processed coded, identified by a study subject number: 6 figures: first three for the participating center and last three for each patient individually. This study subject ID-number will be used on all materials (e.g. blood samples, stool samples, documents) that will eventually leave the study site to the investigator. Patient names, initials or birthdates may not be placed on these materials. In addition, only this number will be used in study documentation, CRF, rapports and publications. The key to the code is safeguarded by the local site investigator or the person this task has been delegated to at each participating study site. People/authorities that are allowed access to the code key are the members of the accredited METC, the Health Inspection, and members from the research team with approval of the principal investigator or head of department. This might be necessary to inspect the accuracy and quality of the study. Direct access to medical records for verification and auditing purposes by the accredited METC, regulatory authorities (e.g. inspectors of the Dutch Health Care Inspectorate), auditors and monitors will be required and permission from each subject will be obtained as part of the consent process. Collected coded data is stored in a secured eCRF (Research Manager) and on a departmental server that is backed-up regularly, safeguarded by a password only available to study team members and with approval of the principal investigator. Collected coded patient material is stored at the local site it was collected at and at the analysis site for short-term storing, and at the Sponsor organization for long-term storing, and is only available to study team members and with approval of the principal investigator.

In case a data security breach takes place the sponsor will notify and report the data breach to the Dutch Data Protection Authority (AP) within 72 hours, using the data leak reporting desk. If the data breach poses a high risk to a study subject(s) affected, then these study subjects will also be informed of the data security breach. In case of a serious data security breach the sponsor will also notify the Member States concerned about the serious data security breach through CTIS, conform section 14.5 of the study protocol.

14.3.2. Source documents and case report forms (CRF)

Source documents for this study will include hospital records in EPIC/HiX and procedure reports and data collection forms (kinetieklijst). These documents will be used to enter data on the eCRF. Data reported on the CRF that are derived from source documents must be consistent with the source documents or the discrepancies must be explained. Electronic Data Capture module from Research Manager will be used as electronic CRF for data collection.

All documents will be stored safely in confidential conditions. On all study-specific documents other than the signed consent, the subject will be referred to by the study subject identification code.

14.3.3. Clinical trial master file and data archiving

The sponsor and the investigator shall keep a clinical trial master file. The clinical trial master file shall at all times contain the essential documents relating to the clinical trial which allow verification of the conduct of a clinical trial and the quality of the data generated.
The sponsor and the investigator shall archive the content of the clinical trial master file for at least 25 years after the end of the clinical trial, unless other EU law requires archiving for a longer period. The medical files of subjects shall be archived in accordance with national law.
The content of the clinical trial master file shall be archived in a way that ensures that it is readily available and accessible, upon request.

14.3.4. Collection and storage of biological samples

All biological samples (blood and kit samples) will be kept confidential and will not be made publicly available. The samples will be coded, identified by a study subject number, as described above (14.3.1).
The total 10 mL of EDTA blood that has been obtained for the routinely performed *DPYD and UGT1A1* genotyping test may after study end in retrospect be used for additional pharmacogenetic analyses. Additionally blood samples (1x10 mL EDTA blood) collected for ctDNA at baseline and follow-up CT scans may be used in retrospect for additional tumor marker analyses. This falls within the scope of this protocol and of related studies. Therefore, coded study samples will be stored for a period of 25 years after study completion. People/authorities that are allowed access to these samples are the members of the accredited METC, the Health Inspection, and members from the research team with approval of the principal investigator.

14.4. Audits and inspections and direct access to source data/documents

This trial may be subject to internal or external monitoring, auditing or inspections procedure to ensure adherence to GCP. Access to all trial-related documents including direct access to source data will be given at that time.

14.5. Reporting of serious breaches

The sponsor will notify the Member States concerned about a serious breach of the Regulation or of the version of the protocol applicable at the time of the breach through CTIS without undue delay but not later than **seven days** of becoming aware of that breach.

14.6. Notification of the start and the end of the recruitment

The sponsor will notify within 15 days each Member State concerned of the start of a clinical trial in relation to that Member State through CTIS.
The sponsor will notify within 15 days each Member State concerned of the first visit of the first subject in relation to that Member State through CTIS.
The sponsor will notify within 15 days each Member State concerned of the end of the recruitment of subjects for a clinical trial in that Member State through the EU.

14.7. Temporary halt/(early) termination

The sponsor will notify within 15 days each Member State concerned of the end of a clinical trial in relation to that Member State through CTIS.

The sponsor will notify within 15 days each Member State concerned of the end of a clinical trial in all Member States concerned and in all third countries in which the clinical trial has been conducted through CTIS.

14.7.1. Temporary halt/early termination for reasons not affecting the benefit-risk balance

The sponsor will notify with 15 days each Member State concerned of a temporary halt of a clinical trial in all Member States concerned for reasons not affecting the benefit-risk balance through CTIS.

When a temporarily halted clinical trial for reasons not affecting the benefit-risk balance is resumed the sponsor will notify each Member State concerned through CTIS.

The sponsor will notify to the EU portal CTIS of early termination of the clinical trial for reasons not affecting the benefit-risk balance through CTIS. The reasons for such action and, when appropriate, follow-up measures for the subjects will be provided as well.

14.7.2. Temporary halt/early termination for reasons of subject safety

In accordance to article 38 of the CTR, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. Sufficient ground is considered if 10% or more of total population have been withdrawn/discontinued from the study due to experienced study burden and if the interim safety analysis performed during PART B shows an increase of >20% severe (grade ≥ 3) toxicity in the PART B population compared to the PART A population and/or if >20% of PART B subjects that received 5-FU dose escalation based on MIPD of 5-FU experienced severe (grade ≥ 3) toxicity. Furthermore, The temporary halt or early termination of a clinical trial for reasons of a change of the benefit-risk balance will be notified to the Member States concerned through the EU portal CTIS without undue delay but not later than in 15 days of the date of the temporary halt or early termination. It shall include the reasons for such action and specify follow-up measures. The restart of the clinical trial following a temporary halt as referred to in paragraph 1 shall be deemed to be a substantial modification subject to the authorisation procedure laid down in Chapter III of the CTR. Individual subjects may be terminated from the study based on physician's discretion, or based on subject's discretion in case the study procedures are experienced as too burdensome.

14.7.2.1. Discontinuation/withdrawal of individual subjects

Individual subjects may be withdrawn from the study based on the treating physician's and investigator's discretion. Study subjects can decide to discontinue participation in the study if they wish to do so without any consequences. FOLFIRINOX treatment may be discontinued at the treating physicians' discretion as part of standard care in the current study, for instance in patients with disease progression that do not respond sufficiently to FOLFIRINOX treatment, or in patients where toxicity-related treatment discontinuation is indicated by the treating physician. In the case of FOLFIRINOX treatment discontinuation as part of standard care procedures, the study subject shall remain part of the clinical study. No more data or material will be collected from withdrawn/discontinued study subjects and follow-up ends on the moment of withdrawal/ discontinuation. When a subject withdraws from a study, the data collected on the subject to the point of withdrawal remains part of the study database and may not be removed.

Withdrawn/discontinued study subjects that have not completed two full cycles of FOLFIRNIOX treatment with related study procedures may be replaced by a new study subject.

14.8. Summary of the results

Within one year from the end of a clinical trial in all Member States concerned, the sponsor will submit to the EU database CTIS a summary of the results of the clinical trial. The content of the summary of the results is set out in CTR Annex IV. It shall be accompanied by a summary written in a manner that is understandable to laypersons. The content of the summary is set out in CTR Annex V.

14.9. Public disclosure and publication policy

Patients are entitled to public disclosure of the results of the study on the basis of their participation in it. The results of study are submitted for publication to peer-reviewed scientific journals and abstracts for scientific conferences. Members of the protocol writing committee will become co-authors. Other investigators actively involved in the execution of the trial will also become co-author to be decided by the protocol writing committee and finally by the study coordinator. All study investigators will be informed in writing prior to any written communication or oral presentation about the study and invited to give comments. In case the number of authors exceeds the maximum number of authors allowed by a journal, authors other than the principal investigators and the coordinating investigator will be listed in a ''List of Collaborators''.

15. REFERENCES

(1) UpToDate: Initial systemtic chemotherapy for metastatic exocrine pancreatic cancer. Available via: Initial systemic chemotherapy for metastatic exocrine pancreatic cancer - UpToDate (Accessed: 24 October 2023).

(2) UpToDate: Initial Chemotherapy and radiation for nonmetastatic, locally advanced, unresectable and borderline resectable exocrine pancreatic cancer. Available via: Initial chemotherapy and radiation for nonmetastatic, locally advanced, unresectable and borderline resectable, exocrine pancreatic cancer - UpToDate. (Accessed: 24 October 2023).

(3) UpToDate: Treatment for potentially resectable exocrine pancreatic cancer. Available via: Treatment for potentially resectable exocrine pancreatic cancer - UpToDate. (Accessed: 24 October 2023).

(4) Conroy T, Pfeiffer P, Vilgrain V, Lamarca A, Seufferlein T, O'Reilly EM, Hackert T, Golan T, Prager G, Haustermans K, Vogel A, Ducreux M; ESMO Guidelines Committee. Pancreatic cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2023 Sep 9:S0923-7534(23)00824-4. doi: 10.1016/j.annonc.2023.08.009.

(5) Gourgou-Bourgade S, Bascoul-Mollevi C, Desseigne F, Ychou M, Bouché O, Guimbaud R, et al. Impact of FOLFIRINOX compared with gemcitabine on quality of life in patients with metastatic pancreatic cancer: results from the PRODIGE 4/ACCORD 11 randomized trial. J Clin Oncol. 2013 Jan 1;31(1):23-9.

(6) Ozaka M, Ishii H, Sato T, Ueno M, Ikeda M, Uesugi K, et al. Cancer Chemother Pharmacol. 2018;81(6):1017. Epub 2018 Apr 9.

(7) Conroy T, Castan F, Lopez A, Turpin A, Ben Abdelghani M, Wei AC, et al. Five-Year Outcomes of FOLFIRINOX vs Gemcitabine as Adjuvant Therapy for Pancreatic Cancer: A Randomized Clinical Trial. JAMA Oncol. 2022 Nov 1;8(11):1571-1578.

(8) Innocenti: Innocenti F, Mills SC, Sanoff H, Ciccolini J, Lenz HJ, Milano G. All you need to know about DPYD genetic testing for patients treated with fluorouracil and capecitabine: a practitioner-friendly guide. JCO Oncol. Pract. 16(12), 793–798 (2020)

(9) Henricks: Henricks LM, Lunenburg C, de Man FM, Meulendijks D, Frederix GWJ, Kienhuis E et al. DPYD genotype-guided dose individualisation of fluoropyrimidine therapy in patients with cancer: a prospective safety analysis. Lancet Oncol. 19(11), 1459–1467 (2018).

(10) Hulshof: Hulshof EC, Deenen MJ, Nijenhuis M, Soree B, de Boer-Veger NJ, Buunk AM et al. Dutch Pharmacogenetics Working Group (DPWG) guideline for the gene-drug interaction between UGT1A1 and irinotecan. Eur. J. Hum. Genet. doi:10.1038/s41431-022-01243-2 (2022).

(11) Amstutz: Amstutz U, Henricks LM, Offer SM, Barbarino J, Schellens JHM, Swen JJ et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Dihydropyrimidine Dehydrogenase Genotype and Fluoropyrimidine Dosing: 2017 Update. Clin. Pharmacol. Ther. 103(2), 210–216 (2018)

(12) Deenen M, Tol J, Burylo A, Doodeman V, de Boer A, Vincent A, e.a. Relationship between single nucleotide polymorphisms and haplotypes in DPYD and toxicity and efficacy of capecitabine in advanced colorectal cancer. Clin Cancer Res. 15 May 2011;17(10):3455–68.

(13) Lunenburg CA, Staveren MC van, Gelderblom H, Guchelaar H-J, Swen JJ. Evaluation of clinical implementation of prospective DPYD genotyping in 5-fluorouracil- or capecitabine-treated patients. Pharmacogenomics. 16 May 2016;17(7):721–9.

(14)Karas S, Innocenti F. All you need to know about UGT1A1 genetic testing for patients treated with irinotecan: a practitioner-friendly guide. JCO Oncol. Pract. 18(4), 270–277 (2022).

(15)Paez D, Tobeña M, Fern ´ andez-Plana J, et al: Pharmacogenetic clinical randomised phase II trial to evaluate the ef ´ ficacy and safety of FOLFIRI with high-dose irinotecan (HD-FOLFIRI) in metastatic colorectal cancer patients according to their UGT1A 1 genotype. Br J Cancer 120:190-195, 2019

(16)Miarons M, Riera P, García-Gil S, Gutiérrez-Nicolás F. Efficacy and safety of high doses of irinotecan in patients with metastatic colorectal cancer treated with the FOLFIRI regimen based on the UGT1A1 genotype: A systematic review. Farm Hosp. 2022 Jul 17;46(4):224-233.

(17)Tsai HL, Huang CW, Lin YW, Wang JH, Wu CC, Sung YC, Chen TL, Wang HM, Tang HC, Chen JB, Ke TW, Tsai CS, Huang HY, Wang JY. Determination of the UGT1A1 polymorphism as guidance for irinotecan dose escalation in metastatic colorectal cancer treated with first-line bevacizumab and FOLFIRI (PURE FIST). Eur J Cancer. 2020 Oct;138:19-29. doi: 10.1016/j.ejca.2020.05.031.

(18)Saam J, Critchfield GC, Hamilton SA, Roa BB, Wenstrup RJ, Kaldate RR. Body Surface Area–based Dosing of 5-Fluoruracil Results in Extensive Interindividual Variability in 5- Fluorouracil Exposure in Colorectal Cancer Patients on FOLFOX Regimens. Clin Colorectal Cancer. 2011.

(19)Gamelin M, Boisdron-Celle M, Guérin-Meyer V, et al. Correlation between uracil and dihydrouracil plasma ratio, fluorouracil (5-FU) pharmacokinetic parameters, and tolerance in patients with advanced colorectal cancer: A potential interest for predicting 5-FU toxicity and determining optimal 5-FU dosage. J Clin Oncol. 1999.

(20)Beumer JH, Chu E, Allegra C, et al. Therapeutic Drug Monitoring in Oncology: International Association of Therapeutic Drug Monitoring and Clinical Toxicology Recommendations for 5-Fluorouracil Therapy. Clin Pharmacol Ther. 2019.

(21)Gamelin E, Delva R, Jacob J, et al. Individual fluorouracil dose adjustment based on pharmacokinetic follow-up compared with conventional dosage: Results of a multicenter randomized trial of patients with metastatic colorectal cancer. J Clin Oncol. 2008.

(22)Gamelin E, Boisdron-Celle M, Delva R, et al. Long-term weekly treatment of colorectal metastatic cancer with fluorouracil and leucovorin: Results of a multicentric prospective trial of fluorouracil dosage optimization by pharmacokinetic monitoring in 152 patients. J Clin Oncol. 1998.

(23)Gamelin EC, Danquechin-Dorval EM, Dumesnil YF, et al. Relationship between 5- fluorouracil (5-FU) dose intensity and therapeutic response in patients with advanced colorectal cancer receiving infusional therapy containing 5-FU. Cancer. 1996.

(24)Li M, Mindt S, Lück A, Hutzschenreuter U, Kollendt M, Lathan B, Zöller T, Frank-Gleich S, Lorentz C, Lamberti C, Sick C, Zingerle M, Tesch H, Stein W, Hebart H, Stosiek C, Sandner R, Fries S, Burkholder I, Hofheinz RD. Drug monitoring detects under- and overdosing in patients receiving 5-fluorouracil-containing chemotherapy-results of a prospective, multicenter German observational study. ESMO Open. 2023 Apr;8(2):101201.

(25)Capitain O, Asevoaia A, Boisdron-Celle M, Poirier AL, Morel A, Gamelin E. Individual

fluorouracil dose adjustment in FOLFOX based on pharmacokinetic follow-up compared with conventional body-area-surface dosing: A phase II, proof-of-concept study. *Clin Colorectal Cancer.* 2012.

(26)Kaldate RR, Haregewoin A, Grier CE, Hamilton SA, McLeod HL. Modeling the 5- Fluorouracil Area Under the Curve Versus Dose Relationship to Develop a Pharmacokinetic Dosing Algorithm for Colorectal Cancer Patients Receiving FOLFOX6. Oncologist. 2012. NL71410.029.19 PERFU_001 Version number: 1.1, Date: 01-10-2019 44 of 44

(27)Wilhelm M, Mueller L, Miller MC, et al. Prospective, Multicenter Study of 5-Fluorouracil Therapeutic Drug Monitoring in Metastatic Colorectal Cancer Treated in Routine Clinical Practice. In: Clinical Colorectal Cancer. ; 2016.

(28)Morawska K, Goirand F, Marceau L, et al. 5-FU therapeutic drug monitoring as a valuable option to reduce toxicity in patients with gastrointestinal cancer. Oncotarget. 2018.

(29)Patel JN, O'Neil BH, Deal AM, et al. A Community-Based Multicenter Trial of Pharmacokinetically Guided 5-Fluorouracil Dosing for Personalized Colorectal Cancer Therapy. Oncologist. 2014.

(30)Capitain O, Asevoaia A, Boisdron-Celle M, Poirier AL, Morel A, Gamelin E. Individual fluorouracil dose adjustment in FOLFOX based on pharmacokinetic follow-up compared with conventional body-area-surface dosing: A phase II, proof-of-concept study. Clin Colorectal Cancer. 2012.

(31)Kline CLB, Schiccitano A, Zhu J, et al. Personalized dosing via pharmacokinetic monitoring of 5-fluorouracil might reduce toxicity in early- or late-stage colorectal cancer patients treated with infusional 5-fluorouracil-based chemotherapy regimens. In: Clinical Colorectal Cancer. ; 2014.

(32)Vilalta-Lacarra A, Aldaz A, Sala-Elarre P, Urrizola A, Chopitea A, Arbea L, et al. Therapeutic drug monitoring of neoadjuvant mFOLFIRINOX in resected pancreatic ductal adenocarcinoma. Pancreatology. 2023 Jun;23(4):411-419.

(33)Fleming GF, Schumm P, Friberg G, Ratain MJ, Njiaju UO, Schilsky RL. Circadian variation in plasma 5-fluorouracil concentrations during a 24 hour constant-rate infusion. *BMC Cancer*. 2015.

(34)Bressolle F, Joulia JM, Pinguet F, Ychou M, Astre C, Duffour J, Gomeni R. Circadian rhythm of 5-fluorouracil population pharmacokinetics in patients with metastatic colorectal cancer. *Cancer Chemother Pharmacol.* 1999.

(35)Deyme L, Barbolosi D, Gattacceca F. Population pharmacokinetics of FOLFIRINOX: a review of studies and parameters. Cancer Chemother Pharmacol. 2019

(36)Hulshof EC, de With M, de Man FM, Creemers GJ, Deiman BALM, Swen JJ, Houterman S, Koolen SLW, Bins S, Thijs AMJ, Laven MMJ, Hövels AM, Luelmo SAC, Houtsma D, Shulman K, McLeod HL, van Schaik RHN, Guchelaar HJ, Mathijssen RHJ, Gelderblom H, Deenen MJ. UGT1A1 genotype-guided dosing of irinotecan: A prospective safety and cost analysis in poor metaboliser patients. Eur J Cancer. 2022 Feb;162:148-157. doi: 10.1016/j.ejca.2021.12.009.

(37)Innocenti F, Schilsky RL, Ram´ırez J, et al: Dose-finding and pharmacokinetic study to optimize the dosing of irinotecan according to the UGT1A1 genotype of patients with cancer. J Clin Oncol 32:2328-2334, 2014

(38)Toffoli G, Cecchin E, Gasparini G, et al: Genotype-driven phase I study of irinotecan administered in combination with fluorouracil/leucovorin in patients with metastatic colorectal cancer. J Clin Oncol 28:866-871, 2010

(39)Marcuello E, Paez D, Par ´ e L, et al: A genotype-directed phase I-IV dose- ´ finding study of irinotecan in combination with fluorouracil/leucovorin as first-line treatment in advanced colorectal cancer. Br J Cancer 105:53-57, 2011

(40)Kim K-P, Hong YS, Lee J-L, et al: A phase I study of UGT1A1 *28/*6 genotype-directed dosing of irinotecan (CPT- 11) in Korean patients with metastatic colorectal cancer receiving FOLFIRI. Oncology 88:164-172, 2015.

(41)Toffoli: Toffoli G, Sharma MR, Marangon E, et al: Genotype-guided dosing study of FOLFIRI plus bevacizumab in patients with metastatic colorectal cancer. Clin Cancer Res 23:918-924, 2017

(42) Lu CY, Huang CW, Hu HM, Tsai HL, Huang CM, Yu FJ, et al. Prognostic advantage of irinotecan dose escalation according to uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) genotyping in patients with metastatic colorectal cancer treated with bevacizumab combined with 5-fluorouracil/leucovorin with irinotecan in a first-line setting. Transl Res. 2014;164(2):169-76.

(43) Phelip JM, Mineur L, De la Fouchardière C, Chatelut E, Quesada JL, Roblin X, et al. High Resectability Rate of Initially Unresectable Colorectal Liver Metastases After UGT1A1-Adapted High-Dose Irinotecan Combined with LV5FU2 and Cetuximab: A Multicenter Phase II Study (ERBIFORT). Ann Surg Oncol. 2016;23(7):2161-6.

(44) Boisdron-Celle M, Metges JP, Capitain O, Adenis A, Raoul JL, Lecomte T, et al. A multicenter phase II study of personalized FOLFIRI-cetuximab for safe dose intensification. Semin Oncol. 2017;44(1):24-33

(45)Hebbar M, Truant S, Desauw C, Sergent-Baudson G, Cattan S, Piessen G, et al. High-dose FOLFIRI, surgery, and radiofrequency ablation for patients with unresectable liver metastases from colorectal cancer. Anticancer Res. 2013;33(4):1603-7.

(46)Manfredi S, Bouché O, Rougier P, Dahan L, Loriot MA, Aparicio T, et al. High-Dose FOLFIRI plus Bevacizumab in the Treatment of Metastatic Colorectal Cancer Patients with Two Different UGT1A1 Genotypes: Mol Cancer Ther. 2015;14(12):2782-8.

(47) G-Standaard. UGT1A1: Irinotecan. Available via: B0001694 (g-standaard.nl). (Accessed: 24 October 2023).

(48) de Man FM, Goey AKL, van Schaik RHN, Mathijssen RHJ, Bins S. Individualization of Irinotecan Treatment: A Review of Pharmacokinetics, Pharmacodynamics, and Pharmacogenetics. Clin Pharmacokinet. 2018 Oct;57(10):1229-1254.

(49) Mathijssen RH, Verweij J, Loos WJ, de Bruijn P, Nooter K, Sparreboom A. Irinotecan pharmacokinetics-pharmacodynamics: the clinical relevance of prolonged exposure to SN-38. Br J Cancer. 2002 Jul 15;87(2):144-50.

(50) Deyme L, Barbolosi D, Mbatchi LC, Tubiana-Mathieu N, Ychou M, Evrard A, Gattacceca F. Population pharmacokinetic model of irinotecan and its four main metabolites in patients treated with FOLFIRI or FOLFIRINOX regimen. Cancer Chemother Pharmacol. 2021 Aug;88(2):247-258.

(51) Chabot GG, Abigerges D, Catimel G, Culine S, de Forni M, Extra JM, et al. Population pharmacokinetics and pharmacodynamics of irinotecan (CPT-11) and active metabolite SN-38 during phase I trials. Ann Oncol. 1995;6(2):141–51.

(52) Klein CE, Gupta E, Reid JM, Atherton PJ, Sloan JA, Pitot HC, et al. Population pharmacokinetic model for irinotecan and two of its metabolites, SN-38 and SN-38 glucuronide. Clin Pharmacol Ther. 2002;72(6):638–47.

(53) Mathijssen RH, Verweij J, de Jonge MJ, Nooter K, Stoter G, Sparreboom A. Impact of body-size measures on irinotecan clearance: alternative dosing recommendations. J Clin Oncol. 2002;20(1):81–7.

(54) Berg AK, Buckner JC, Galanis E, Jaeckle KA, Ames MM, Reid JM. Quantification of the impact of enzyme-inducing antiepileptic drugs on irinotecan pharmacokinetics and SN-38 exposure. J Clin Pharmacol. 2015;55(11):1303–12.

(55) Gupta E, Mick R, Ramirez J, Wang X, Lestingi TM, Vokes EE, et al. Pharmacokinetic and pharmacodynamic evaluation of the topoisomerase inhibitor irinotecan in cancer patients. J Clin Oncol. 1997;15(4):1502–10.

(56) de Jong FA, Mathijssen RH, Xie R, Verweij J, Sparreboom A. Flat-fixed dosing of irinotecan: influence on pharmacokinetic and pharmacodynamic variability. Clin Cancer Res. 2004;10(12 Pt 1):4068–71.

(57) Gupta E, Lestingi TM, Mick R, Ramirez J, Vokes EE, Ratain MJ. Metabolic fate of irinotecan in humans: correlation of glucuronidation with diarrhea. Cancer Res. 1994;54(14):3723–5.

(58) Mick R, Gupta E, Vokes EE, Ratain MJ. Limited-sampling models for irinotecan pharmacokinetics-pharmacodynamics: prediction of biliary index and intestinal toxicity. J Clin Oncol. 1996;14(7):2012–9.

(59) Herben VM, Schellens JH, Swart M, Gruia G, Vernillet L, Beijnen JH, et al. Phase I and pharmacokinetic study of irinotecan administered as a low-dose, continuous intravenous infusion over 14 days in patients with malignant solid tumors. J Clin Oncol. 1999;17(6):1897–905

(60) de Jonge MJ, Verweij J, de Bruijn P, Brouwer E, Mathijssen RH, van Alphen RJ, et al. Pharmacokinetic, metabolic, and pharmacodynamic profiles in a dose-escalating study of irinotecan and cisplatin. J Clin Oncol. 2000;18(1):195–203.

(61) Canal P, Gay C, Dezeuze A, Douillard JY, Bugat R, Brunet R, et al. Pharmacokinetics and pharmacodynamics of irinotecan during a phase II clinical trial in colorectal cancer. Pharmacology and molecular mechanisms group of the European Organization for Research and Treatment of Cancer. J Clin Oncol. 1996;14(10):2688–95.

(62) Oyaga-Iriarte E, Insausti A, Sayar O, Aldaz A. Population pharmacokinetic model of irinotecan and its metabolites in patients with metastatic colorectal cancer. Eur J Clin Pharmacol 2019;75:529e42.

(63) Garufi C, Torsello A, Tumolo S, Ettorre GM, Zeuli M, Campanella C, et al. Cetuximab plus chronomodulated irinotecan, 5-fluorouracil, leucovorin and oxaliplatin as neoadjuvant chemotherapy in colorectal liver metastases: POCHER trial. Br J Cancer. 2010;103(10):1542–7.

(64) Gholam D, Giacchetti S, Brezault-Bonnet C, Bouchahda M, Hauteville D, Adam R, et al. Chronomodulated irinotecan, oxaliplatin, and leucovorin-modulated 5-Fluorouracil as

ambulatory salvage therapy in patients with irinotecan- and oxaliplatin-resistant metastatic colorectal cancer. Oncologist. 2006;11(10):1072–80.

(65) Garufi C, Vanni B, Aschelter AM, Zappala AR, Bria E, Nistico C, et al. Randomised phase II study of standard versus chronomodulated CPT-11 plus chronomodulated 5-fluorouracil and folinic acid in advanced colorectal cancer patients. Eur J Cancer. 2006;42(5):608–16.

(66) Levi F, Okyar A, Dulong S, Innominato PF, Clairambault J. Circadian timing in cancer treatments. Annu Rev Pharmacol Toxicol. 2010;50:377–421.

(67) Longley DB, Harkin DP, Johnston PG. 5-Fluorouracil: Mechanisms of action and clinical strategies. Nat Rev Cancer. 2003.

(68) Heggie GD, Sommadossi JP, Cross DS, Huster WJ. Clinical Pharmacokinetics of 5- Fluorouracil and Its Metabolites in Plasma, Urine, and Bile. Cancer Res. 1987.

(69) Ehrsson H, Wallin I, Yachnin J. Pharmacokinetics of oxaliplatin in humans. Med Oncol. 2002;19(4):261-5. doi: 10.1385/MO:19:4:261.

(70) Lurvink RJ, Tajzai R, Rovers KP, Wassenaar ECE, Moes DAR, Pluimakers G, Boerma D, Burger JWA, Nienhuijs SW, de Hingh IHJT, Deenen MJ. Systemic Pharmacokinetics of Oxaliplatin After Intraperitoneal Administration by Electrostatic Pressurized Intraperitoneal Aerosol Chemotherapy (ePIPAC) in Patients with Unresectable Colorectal Peritoneal Metastases in the CRC-PIPAC Trial. Ann Surg Oncol. 2021 Jan;28(1):265-272. doi: 10.1245/s10434-020-08743-9.

(71) RECIST: 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- 247. doi:10.1016/j.ejca.2008.10.02.

(72) van Dijk DP, Bakens MJ, Coolsen MMM, et al. Low skeletal muscle radiation attenuation and visceral adiposity are associated with overall survival and surgical site infections in patients with pancreatic cancer. *Journal of cachexia, sarcopenia and muscle* 2017; 8(2): 317-26.

(73) Fearon K, Strasser F, Anker SD, et al. Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol* 2011; 12(5): 489-95.

(74) Arends J, Bachmann P, Baracos V, et al. ESPEN guidelines on nutrition in cancer patients. *Clin Nutr* 2017; 36(1): 11-48.

(75) Black D, Mackay C, Ramsay G, et al. Prognostic Value of Computed Tomography: Measured Parameters of Body Composition in Primary Operable Gastrointestinal Cancers. *Ann Surg Oncol* 2017; 24(8): 2241-51.

(76) Grossberg AJ, Chamchod S, Fuller CD, et al. Association of Body Composition With Survival and Locoregional Control of Radiotherapy-Treated Head and Neck Squamous Cell Carcinoma. *JAMA oncology* 2016; 2(6): 782-9.

(77) Bundred J, Kamarajah SK, Roberts KJ. Body composition assessment and sarcopenia in patients with pancreatic cancer: a systematic review and meta-analysis. *HPB (Oxford)* 2019; 21(12): 1603-12.

(78) Van Dijk DP, Krill M, Farshidfar F, et al. Host phenotype is associated with reduced survival independent of tumor biology in patients with colorectal liver metastases. *Journal of Cachexia, Sarcopenia and Muscle* 2018.

(79) Ackermans L, Volmer L, Wee L, et al. Deep Learning Automated Segmentation for Muscle and Adipose Tissue from Abdominal Computed Tomography in Polytrauma Patients. *Sensors (Basel, Switzerland)* 2021; 21(6).

(80) Grunvald MW, Jacobson RA, Kuzel TM, Pappas SG, Masood A. Current Status of Circulating Tumor DNA Liquid Biopsy in Pancreatic Cancer. Int J Mol Sci. 2020 Oct 16;21(20):7651. doi: 10.3390/ijms21207651.

(81) Jonsson EN, Karlsson MO. Xpose--an S-PLUS based population pharmacokinetic/pharmacodynamic model building aid for NONMEM. *Comput Methods Programs Biomed*. Jan 1999;58(1):51-64. doi:10.1016/s0169-2607(98)00067-4

(82) Lindbom L, Pihlgren P, Jonsson EN. PsN-Toolkit--a collection of computer intensive statistical methods for non-linear mixed effect modeling using NONMEM. *Comput Methods Programs Biomed*. Sep 2005;79(3):241-57. doi:10.1016/j.cmpb.2005.04.005

(83) Beal S SL, Boeckmann A. NONMEM user's guides Ellicott City: ICON Development Solutions. Updated 2006.

(84) Keizer RJ, van Benten M, Beijnen JH, Schellens JH, Huitema AD. Piraña and PCluster: a modeling environment and cluster infrastructure for NONMEM. *Comput Methods Programs Biomed*. Jan 2011;101(1):72-9. doi:10.1016/j.cmpb.2010.04.018

(85) Team RDC. R: a language and environment for statistical computing. Vienna: R Foundation for Statistical Computing.

(86) da Silva LC, Grando AP, de Baco LS, Hahn RZ, Ferreira Filho AF, Brucker N, et al. Evaluation of dried blood spots as an alternative sampling strategy for 5-fluorouracil monitoring: From method development to clinical application. J Pharm Biomed Anal. 2023 Oct 25;235:115539.

(87) Radovanovic M, Schneider JJ, Shafiei M, Martin JH, Galettis P. Measurement of 5-fluorouracil, capecitabine and its metabolite concentrations in blood using volumetric absorptive microsampling technology and LC-MS/MS. J Chromatogr B Analyt Technol Biomed Life Sci. 2022 Jan 1;1188:123075.

(88) Bhatt AP et al. Targeted inhibition of gut bacterial β-glucuronidase activity enhances anticancer drug efficacy. Proc Natl Acad Sci U S A. 2020 Mar 31;117(13):7374-7381.

(89) Wallace BD, et al. Alleviating cancer drug toxicity by inhibiting a bacterial enzyme. Science. 2010 Nov 5;330(6005):831-5.

(90)Watanabe K, Nakamura T, Kimura Y, Motoya M, Kojima S, Kuraya T, et al. Tumor-Informed Approach Improved ctDNA Detection Rate in Resected Pancreatic Cancer. Int J Mol Sci. 2022 Sep 29;23(19):11521.

(91) Capiau S, Veenhof H, Koster RA, Bergqvist Y, Boettcher M, Halmingh O, et al. Official International Association for Therapeutic Drug Monitoring and Clinical Toxicology Guideline: Development and Validation of Dried Blood Spot-Based Methods for Therapeutic Drug Monitoring. Ther Drug Monit. 2019 Aug;41(4):409-30.

(92)Mould DR, Upton RN. Basic concepts in population modeling, simulation, and model-based drug development-part 2: introduction to pharmacokinetic modeling methods. CPT Pharmacometrics Syst Pharmacol. 2013 Apr 17;2(4):e38.

APPENDIX I: FOLFIRINOX (klassiek) poliklinisch (Catharina Ziekenhuis Eindhoven)

BEHANDELSCHEMA FOLFIRINOX (klassiek) poliklinisch (voorbeeld Catharina Ziekenhuis Eindhoven)

Uw arts heeft u voorgesteld om uw ziekte te behandelen met chemotherapie. Het behandelschema bestaat uit de geneesmiddelen Folinezuur, Fluorouracil, Irinotecan en Oxaliplatine en wordt FOLFIRINOX genoemd.

Het doel van het behandelschema is om de groei van de kankercel te remmen, te zorgen dat de kankercel niet meer kan delen en uw klachten te verminderen.

Folinezuur, Fluorouracil, Irinotecan en Oxaliplatine
U krijgt dit behandelschema elke 2 weken toegediend. Na 3-4 kuren vindt er een evaluatie plaats en afhankelijk van deze uitslag wordt het vervolg van de behandeling bepaald.
De toediening van de Oxaliplatine, Irinotecan and folinezuur via het infuus duurt ongeveer 2,5 uur. De Fluorouracil krijgt u eerst in een kortdurend infuus van 5 minuten. Dit alles vindt poliklinisch plaats op de dagbehandeling Oncologie. Aansluitend gaat u met de medicatie Fluorouracil, via een cassette en een draagbare CADD-pomp, gedurende ongeveer 46 uur toegediend, naar huis. Na 46 uur komt u terug naar de dagbehandeling Oncologie en wordt de cassette afgekoppeld. Hierover krijgt u specifieke voorlichting.
Het is goed u te realiseren dat voor u persoonlijk de situatie anders kan zijn dan hier omschreven. Uw arts zal dit dan met u bespreken.

Medicatie
Tijdens de behandeling kunt u last krijgen van misselijkheid. Om dit zoveel mogelijk te voorkomen krijgt u aanvullende medicijnen:

- Dexamethason: 1 keer per dag 8 mg (2 tabletten van 4 mg) om 8.00 uur gedurende 3 dagen, vanaf dag 1 van de kuur.
- Granisetron (Kytril): 1 x per dag 1 tablet van 2mg, om 8:00 uur op de dag van de kuur.
- Atropine injectie: u krijgt voor de toediening van Irinotecan een injectie onder de huid. Dit is om de bijwerkingen van Irinotecan tegen te gaan of eventuele klachten te verminderen.

		Week 1							Week 2						
	Kuur Folinezuur + Fluorouracil + Irinotecan + Oxaliplatine Dag (datum)	1	2	3	4	5	6	7	8	9	10	11	12	13	14
	Atropine via injectie onder de huid	**X**													
	Oxaliplatine via infuus	**X**													
	Irinotecan via infuus (tegelijk met Oxaliplatine)	**X**													

	Folinezuur via infuus (na Irinotecan, tegelijk met Oxaliplatine)	**X**													
	Fluorouracil via infuus en cassette	**X**	**X**												
	Dexamethason tabletten	**X**	**X**	**X**											
	Granisetron tablet	**X**													

In het schema hierboven kunt u zien op welke dagen welke medicijnen worden gegeven of dienen te worden ingenomen.

Bijwerkingen

Hieronder vindt u een opsomming van de meest voorkomende bijwerkingen van deze kuur. Deze bijwerkingen treden niet bij iedereen op en wisselen sterk van ernst.

Algemene bijwerkingen:

- Vermindering van alle bloedcellen, waardoor vatbaarder voor infecties, kans op blauwe plekken/bloedingen en op bloedarmoede.
- Misselijkheid, braken en smaakverandering en hierdoor mogelijk een gebrek aan eetlust
- Ontsteking en irritatie van het mondslijmvlies
- Vermoeidheid, toenemend in de loop van de kuren

Oxaliplatine: oxaliplatine | Apotheek.nl

- Gevoelloosheid of tintelingen in vingers of tenen, welke beïnvloed wordt door koude. Soms kan er tijdens of vlak na de toediening van oxaliplatine een gespannen gevoel in de keel of hals ontstaan. Dit gevoel is van voorbijgaande aard, de ademhaling gaat gewoon door.
- Tijdens de behandelperiode kunt u extra gevoelig zijn voor koude (bijvoorbeeld lage temperaturen en koude dranken).
- Tijdens de toediening kan de infuusarm pijn doen.

Irinotecan: irinotecan | Apotheek.nl

- Tijdens of vlak na het toedienen van de kuur: buikkramp, transpireren, tranende ogen, wazig zien, trage hartslag, diarree. Belangrijk om bij optreden van een of meerdere verschijnselen meteen uw verpleegkundige te waarschuwen. U krijgt dan medicatie toegediend waardoor de verschijnselen meteen opgeheven worden.
- Late diarree (langer dan 48 uur na toediening medicatie)
- Haaruitval kan optreden

Fluorouracil: fluorouracil | Apotheek.nl

- **Pijnlijke mond, tong of keel**.
- Maagdarmklachten (diarree, buik- en/of maagpijn)
- Een hand-voet huidreactie (handpalmen of voetzolen tintelen, dof gevoel, pijnlijk, gezwollen of rood) huiduitslag, droge of jeukende huid, blaren, vervelling.

Aanvullende medicatie:

Atropine: atropine om in te nemen | Apotheek.nl

- Maagdarmklachten

- Droge mond/neus/ogen
- Hartkloppingen

Dexamethason: dexamethason | Apotheek.nl
- Onrust en slapeloosheid
- De eetlust kan tijdelijk groter worden
- Rode blos op de wangen. Het is een onschuldige bijwerking en verdwijnt spontaan na 1-2 dagen
- Maagklachten

Folinezuur: folinezuur | Apotheek.nl
- Misselijk
- Braken
- Diarree
- Slapeloosheid

Granisetron: granisetron | Apotheek.nl
- Hoofdpijn
- Obstipatie

Overige aandachtspunten:
- Bij deze kuur zitten gedurende 7 dagen afbraakproducten in urine en ontlasting en bij mannen in het sperma. U dient hiermee rekening te houden bij uw toiletgang en hygiëne.
- Tijdens chemotherapie kun je vette vis eten. Vette vis is een belangrijke bron van eiwit en energie. Visvetzuren zijn goed voor hart en bloedvaten.
  Supplementen met visolie worden afgeraden vanaf 24 uur vóór, tot en met 24 uur ná de toediening van de specifieke middelen Oxaliplatine en Irinotecan. De reden hiervoor is dat visoliesupplementen hoge concentraties van een specifiek vetzuur (PIFA) kunnen bevatten, wat mogelijk een negatief effect heeft op de behandeling.

ROADMAP
Behandelwijzer FOLFIRINOX (klassiek) poliklinisch (voorbeeld Catharina Ziekenhuis Eindhoven)

KUURSCHEMA

Cytostatica	1	2	3	4	5	6	7	8	9	10	11	12	13	14	**Tijdsduur infusie**
OXALIPLATIN 85mg/m2 Glucose 5% intraveneus	X														120 minuten
IRINOTECAN 150mg/m2 NaCl 0,9% intraveneus	X														90 minuten
FLUOROURACIL 400mg/m2NaCl 0,9% intraveneus	X														2-4 minuten
FLUOROURACIL 2400mg/m2NaCl 0,9% intraveneus	X	X													46 uur (geleverd in 2 zakken of 1 cassette)
Co-medicatie	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
FOLINEZUUR 400mg/m2 Glucose 5% intraveneus	X														15 minuten

Profylaxe	**Toelichting**
ATROPINE, 1xdgs 0,25mg,subcutaan	Voorafgaand aan toediening IRINOTECAN. Indien acuut cholinergisch syndroom bij eerderetoediening, dosering zo nodig aanpassen naar 0,5mg subcutaan.

Anti-emetica	1	2	3	4	5	6	7	8	9	10	11	12	13	14
DEXAMETHASON, 8mg, tablet, oraal	X	X	X											
GRANISETRON, 2mg, tablet, oraal	X													

Medicatie	**Toelichting**

CIPROXIN, 2xdgs 500mg,oraal	Toevoegen als diarree na 24 uur loperamide nietover is.

TOEPASSING

- Kuur wordt 1 x per 2 weken palliatief gegeven aan patiënten met gemetastaseerd pancreascarcinoom met een goede performance status of met een colorectaal carcinoom. Maximaal 12 kuren
- Kuur wordt gegeven aan patiënten met een (borderline) resectabel pancreascarcinoom . Na 4 kuren wordt er een CT ter evaluatie gemaakt. Bij progressie of metastasering krijgt patiënt palliatieve zorg, anders volgen nogmaals 4 kuren folfirinox. Chirurgische resectie vindt plaats 3 tot 6 weken na afloop chemotherapie. Adjuvante behandeling vindt niet plaats in de interventiegroep.

BELEID

- Bepaling DPYD genotypering voor start 5-FU. De apotheek voorziet in het laboratoriumsysteem de genotypering van een doseringsadvies.
- Bepaling UGT1A1 genotypering voor start irinotecan. De apotheek voorziet in het laboratoriumsysteem de genotypering van een doseringsadvies.
- Atropine, 0,25 mg subcutaan standaard voor aanvang van irinotecan gegeven vanwege het acuut cholinergisch syndroom. Zonodig mag het tijdens infusie éénmaal herhaald worden
- Bij patiënten bij wie zich acute laryngopharyngeale dysesthesie voordoet tijdens of binnen enkele uren na een 2 uur durend oxaliplatin infuus, dient de volgende infusie over een periode van 6 uur toegediend te worden.
- Ter voorkoming van koorts na toediening oxaliplatin op dag 1 4x1000 mg paracetamol per os of supp. Toedienen
- De patiënt krijgt een recept mee voor loperamide (Arestal®, Imodium®), voor het eventueel optreden van late diarree. De loperamide dient de patiënt bij voorbaat in huis te halen.
- De patiënt krijgt een recept mee voor antibioticum (Ciproxin®). Deze tabletten hoeft de patiënt nog niet in huis te halen.
- Bij late diarree start patiënt met innemen loperamide, de eerste keer 2 tabletten/capsules en vervolgens iedere 2 uur 1 tablet/capsule. De loperamide dient te blijven worden ingenomen tot 12 uur na het optreden van de laatste diarree. De loperamide mag niet langer dan 48 uur worden ingenomen.
- De patiënt dient na 24 uur diarree naast de loperamide te starten met Ciproxin®.
- Ter preventie hand-voet syndroom krijgt patiënt het advies om twee keer per dag de handen en voeten in te smeren.
- Zorg voor goede anticonceptie

ANTI-EMETICA BELEID

Stap 4: anti-emeticabeleid bij chemotherapie

WERKWIJZE

- Zie controlelijst
- Atropine 0,25 mg subcutaan toedienen voor irinotecan infusie. Zo nodig mag het tijdens infusie éénmaal herhaald worden.
- Het inlopen van oxaliplatin (in 120 min) wordt gecombineerd met eerst gelijktijdig de toediening van irinotecan (in 90 min) en daarna folinezuur (in 15 min). Hiervoor dienen wel alle middelen te zijn verdund in glucose 5% (toediening van oxaliplatin nooit combineren met NaCl0,9%).
- Op het infuus worden 2 chemolijnen aangesloten. De 1e lijn is voor de oxaliplatin en de 5-FU de 2 e lijn voor de irinocecan en de folinezuur.

- De toedienvolgorde is als volgt: Op lijn 1 start met de oxaliplatin in 120 minuten, gevolgd door de 5-FU bolus in 2-4 minuten. Na de bolus de venflon of PICC / VAP naspoelen met 20ml NACL 0,9% en vervolgens de 5-FU zakken of cassette aansluiten. Op lijn 2 start met de irinotecan in 90 minuten, daarna de leucovorin in 15 minuten toedienen.
- De 46u lopende 5-FU wordt in 2 zakken aangeleverd of in 1 cassette.
- 5-FU 46 uur infuus kan ook via ambulant pompsysteem toegediend worden; via VAP / PICC en CADD-one pomp.
- De 5-FU voor de CADD pomp wordt standaard geleverd in 1 CADD-250ml-cassette met daarin de gehele dosis verdund in 200ml.

OPMERKINGEN
- Noodset (Atropine, 0,25 mg subcutaan) dient bij patiënt op kamer aanwezig te zijn voor het eventueel optreden van het acuut cholinergisch syndroom.
- Het infuus met irinotecan dient te worden beschermd tegen licht, dit geldt alleen voor de infuuszak, niet voor het systeem.
- Oxaliplatin wordt opgelost in een glucose 5% oplossing. **Niet mengen of gelijktijdig toedienen met zoutoplossingen of andere oplossingen die chloride bevatten.**
- Geen aluminium bevattende hulpmiddelen (bijvoorbeeld naalden) gebruiken, in verband met het risico op vorming van neerslag ondermeer bestaande uit platina.
- In verband met risico op duizeligheid mag patiënt 24 uur na toediening niet zelf autorijden.
- In combinatie met leucovorin ontstaat een potentiëring van de anti-tumor activiteit van 5-FU.
- Bij patiënten die gaan starten met 5-FU, tegafur of capecitabine vindt er bepaling plaats van de *DPYD* genotypering. *DPYD* is het gen dat codeert voor het enzym dihydropyrimidine dehydrogenase (DPD). Variaties in het gen *DPYD* kunnen leiden tot een verlaagde of afwezige enzymactiviteit. Fluorouracil wordt voor meer dan 80% door het enzym DPD omgezet in de inactieve metaboliet dihydrofluorouracil. Een lagere metabole activiteit van DPD leidt tot verhoogde intracellulaire concentraties van fluorodeoxyuridinemonofosfaat, de actieve metaboliet van fluorouracil en diens prodrug capecitabine. Hierdoor neemt het risico op bijwerkingen als neutropenie, trombopenie, hand-foot-syndroom en mucositis toe. In de Kaukasische populatie heeft ongeveer 3-5% een partiële DPD-deficiëntie en 0,1-0,2% een volledige DPD deficiëntie. In de Afrikaans-Amerikaanse populatie heeft ongeveer 8% een partiële DPD-deficiëntie.
- Voorafgaand aan irinotecan behandeling vindt *UGT1A1*-genotypering plaats. Bijwerkingen van irinotecan treden significant vaker op bij patiënten die homozygoot drager zijn van *UGT1A1**28, *UGT1A1**93, en *UGT1A1**6 doordat deze genvarianten tot verminderde glucuronidering en daarmee tot hogere concentraties van de actieve metaboliet SN-38 leiden.

EXCRETA
5 dagen besmet vanaf dag 1

BIJWERKINGEN
- beenmergdepressie (na ± 8 dagen)
- misselijkheid en braken
- diarree, late diarree (meestal rond vijfde dag)
- stomatitis / mucositis
- volledige haaruitval
- acuut cholinergisch syndroom (vroege diarree, buikpijn, conjunctivitis, rhinitis, hypotensie, vasodilatatie, transpiratie, rillingen, malaise, duizeligheid, visusstoornissen, tranenvloed en speekselvloed)

- korte termijn neurotoxiciteit; acute laryngopharyngeale dysesthesie (subjectief gevoel van dysfagie en dyspnoe zonder objectief bewijs voor ademhalingsmoeilijkheden. Syndroom, veelal uitgelokt of verergerd door koude, is binnen enkele minuten reversibel)
- lange termijn neurotoxiciteit ;sensorische perifere neuropathie, veelal uitgelokt of verergerd door koude. Incidentie en ernst neemt toe bij stijging cumulatieve dosis
- ontsteking of zwelling op de plaats van het infuus
- flebitis; vaak met bruine verkleuring van de huid ter plaatse
- obstipatie
- hand-voet syndroom (rode en pijnlijke huid)
- allergische huidreacties
- abnormale pigmentatie, acné
- oogtoxiciteit (droge of tranende ogen)
- leverfunctiestoornissen
- cardiotoxiciteit
- risico op infertiliteit

APPENDIX II: modified-FOLFIRINOX poliklinisch (Catharina Ziekenhuis Eindhoven)

BEHANDELSCHEMA modified-FOLFIRINOX poliklinisch (voorbeeld Catharina Ziekenhuis Eindhoven)

Uw arts heeft u voorgesteld om uw ziekte te behandelen met chemotherapie. Het behandelschema bestaat uit de geneesmiddelen Folinezuur, Fluorouracil, Irinotecan en Oxaliplatine en wordt FOLFIRINOX genoemd.

Het doel van het behandelschema is om de groei van de kankercel te remmen, te zorgen dat de kankercel niet meer kan delen en uw klachten te verminderen.

Folinezuur, Fluorouracil, Irinotecan en Oxaliplatine
U krijgt dit behandelschema elke 2 weken toegediend. Na 3-4 kuren vindt er een evaluatie plaats en afhankelijk van deze uitslag wordt het vervolg van de behandeling bepaald.
De toediening van de Oxaliplatine, Irinotecan and folinezuur via het infuus duurt ongeveer 2,5 uur. Dit alles vindt poliklinisch plaats op de dagbehandeling Oncologie. Aansluitend gaat u met de medicatie Fluorouracil, via een cassette en een draagbare CADD-pomp, gedurende ongeveer 46 uur toegediend, naar huis. Na 46 uur komt u terug naar de dagbehandeling Oncologie en wordt de cassette afgekoppeld. Hierover krijgt u specifieke voorlichting.
Het is goed u te realiseren dat voor u persoonlijk de situatie anders kan zijn dan hier omschreven. Uw arts zal dit dan met u bespreken.

Medicatie
Tijdens de behandeling kunt u last krijgen van misselijkheid. Om dit zoveel mogelijk te voorkomen krijgt u aanvullende medicijnen:

- Dexamethason: 1 keer per dag 8 mg (2 tabletten van 4 mg) om 8.00 uur gedurende 3 dagen, vanaf dag 1 van de kuur.
- Granisetron (Kytril): 1 x per dag 1 tablet van 2mg, om 8:00 uur op de dag van de kuur.
- Atropine injectie: u krijgt voor de toediening van Irinotecan een injectie onder de huid. Dit is om de bijwerkingen van Irinotecan tegen te gaan of eventuele klachten te verminderen.

		Week 1							Week 2						
	Kuur Folinezuur + Fluorouracil + Irinotecan + Oxaliplatine Dag (datum)	1	2	3	4	5	6	7	8	9	10	11	12	13	14
	Atropine via injectie onder de huid	**X**													
	Oxaliplatine via infuus	**X**													
	Irinotecan via infuus (tegelijk met Oxaliplatine)	**X**													
	Folinezuur via infuus (na Irinotecan, tegelijk met Oxaliplatine)	**X**													

	Fluorouracil via infuus en cassette	**X**	**X**												
	Dexamethason tabletten	**X**	**X**	**X**											
	Granisetron tablet	**X**													

In het schema hierboven kunt u zien op welke dagen welke medicijnen worden gegeven of dienen te worden ingenomen.

Bijwerkingen

Hieronder vindt u een opsomming van de meest voorkomende bijwerkingen van deze kuur. Deze bijwerkingen treden niet bij iedereen op en wisselen sterk van ernst.

Algemene bijwerkingen:

- Vermindering van alle bloedcellen, waardoor vatbaarder voor infecties, kans op blauwe plekken/bloedingen en op bloedarmoede.
- Misselijkheid, braken en smaakverandering en hierdoor mogelijk een gebrek aan eetlust
- Ontsteking en irritatie van het mondslijmvlies
- Vermoeidheid, toenemend in de loop van de kuren

Oxaliplatine: oxaliplatine | Apotheek.nl

- Gevoelloosheid of tintelingen in vingers of tenen, welke beïnvloed wordt door koude. Soms kan er tijdens of vlak na de toediening van oxaliplatine een gespannen gevoel in de keel of hals ontstaan. Dit gevoel is van voorbijgaande aard, de ademhaling gaat gewoon door.
- Tijdens de behandelperiode kunt u extra gevoelig zijn voor koude (bijvoorbeeld lage temperaturen en koude dranken).
- Tijdens de toediening kan de infuusarm pijn doen.

Irinotecan: irinotecan | Apotheek.nl

- Tijdens of vlak na het toedienen van de kuur: buikkramp, transpireren, tranende ogen, wazig zien, trage hartslag, diarree. Belangrijk om bij optreden van een of meerdere verschijnselen meteen uw verpleegkundige te waarschuwen. U krijgt dan medicatie toegediend waardoor de verschijnselen meteen opgeheven worden.
- Late diarree (langer dan 48 uur na toediening medicatie)
- Haaruitval kan optreden

Fluorouracil: fluorouracil | Apotheek.nl

- **Pijnlijke mond, tong of keel**.
- Maagdarmklachten (diarree, buik- en/of maagpijn)
- Een hand-voet huidreactie (handpalmen of voetzolen tintelen, dof gevoel, pijnlijk, gezwollen of rood) huiduitslag, droge of jeukende huid, blaren, vervelling.

Aanvullende medicatie:

Atropine: atropine om in te nemen | Apotheek.nl

- Maagdarmklachten
- Droge mond/neus/ogen
- Hartkloppingen

Dexamethason: dexamethason | Apotheek.nl
- Onrust en slapeloosheid
- De eetlust kan tijdelijk groter worden
- Rode blos op de wangen. Het is een onschuldige bijwerking en verdwijnt spontaan na 1-2 dagen
- Maagklachten

Folinezuur: folinezuur | Apotheek.nl
- Misselijk
- Braken
- Diarree
- Slapeloosheid

Granisetron: granisetron | Apotheek.nl
- Hoofdpijn
- Obstipatie

Overige aandachtspunten:
- Bij deze kuur zitten gedurende 7 dagen afbraakproducten in urine en ontlasting en bij mannen in het sperma. U dient hiermee rekening te houden bij uw toiletgang en hygiëne.
- Tijdens chemotherapie kun je vette vis eten. Vette vis is een belangrijke bron van eiwit en energie. Visvetzuren zijn goed voor hart en bloedvaten.
  Supplementen met visolie worden afgeraden vanaf 24 uur vóór, tot en met 24 uur ná de toediening van de specifieke middelen Oxaliplatine en Irinotecan. De reden hiervoor is dat visoliesupplementen hoge concentraties van een specifiek vetzuur (PIFA) kunnen bevatten, wat mogelijk een negatief effect heeft op de behandeling.

ROADMAP
Behandelwijzer modified-FOLFIRINOX poliklinisch (voorbeeld Catharina Ziekenhuis Eindhoven)

KUURSCHEMA

Cytostatica	1	2	3	4	5	6	7	8	9	10	11	12	13	14	**Tijdsduur infusie**
OXALIPLATIN 85mg/m2 Glucose 5% intraveneus	X														120 minuten
IRINOTECAN 150mg/m2 NaCl 0,9% intraveneus	X														90 minuten
FLUOROURACIL 2400mg/m2NaCl 0,9% intraveneus	X	X													46 uur (geleverd in 2 zakken of 1 cassette)
Co-medicatie	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
FOLINEZUUR 400mg/m2 Glucose 5% intraveneus	X														15 minuten

Profylaxe	**Toelichting**
ATROPINE, 1xdgs 0,25mg,subcutaan	Voorafgaand aan toediening IRINOTECAN. Indien acuut cholinergisch syndroom bij eerderetoediening, dosering zo nodig aanpassen naar 0,5mg subcutaan.

Anti-emetica	1	2	3	4	5	6	7	8	9	10	11	12	13	14
DEXAMETHASON, 8mg, tablet, oraal	X	X	X											
GRANISETRON, 2mg, tablet, oraal	X													

Medicatie	**Toelichting**
CIPROXIN, 2xdgs 500mg,oraal	Toevoegen als diarree na 24 uur loperamide nietover is.

TOEPASSING
- Kuur wordt 1 x per 2 weken palliatief gegeven aan patiënten met gemetastaseerd pancreascarcinoom met een goede performance status of met een colorectaal carcinoom. Maximaal 12 kuren
- Kuur wordt gegeven aan patiënten met een (borderline) resectabel pancreascarcinoom . Na 4 kuren wordt er een CT ter evaluatie gemaakt. Bij progressie of metastasering krijgt patiënt palliatieve zorg, anders volgen nogmaals 4 kuren folfirinox. Chirurgische resectie vindt plaats 3 tot 6 weken na afloop chemotherapie. Adjuvante behandeling vindt niet plaats in de interventiegroep.

BELEID
- Bepaling DPYD genotypering voor start 5-FU. De apotheek voorziet in het laboratoriumsysteem de genotypering van een doseringsadvies.
- Bepaling UGT1A1 genotypering voor start irinotecan. De apotheek voorziet in het laboratoriumsysteem de genotypering van een doseringsadvies.
- Atropine, 0,25 mg subcutaan standaard voor aanvang van irinotecan gegeven vanwege het acuut cholinergisch syndroom. Zonodig mag het tijdens infusie éénmaal herhaald worden
- Bij patiënten bij wie zich acute laryngopharyngeale dysesthesie voordoet tijdens of binnen enkele uren na een 2 uur durend oxaliplatin infuus, dient de volgende infusie over een periode van 6 uur toegediend te worden.
- Ter voorkoming van koorts na toediening oxaliplatin op dag 1 4x1000 mg paracetamol per os of supp. Toedienen
- De patiënt krijgt een recept mee voor loperamide (Arestal®, Imodium®), voor het eventueel optreden van late diarree. De loperamide dient de patiënt bij voorbaat in huis te halen.
- De patiënt krijgt een recept mee voor antibioticum (Ciproxin®). Deze tabletten hoeft de patiënt nog niet in huis te halen.
- Bij late diarree start patiënt met innemen loperamide, de eerste keer 2 tabletten/capsules en vervolgens iedere 2 uur 1 tablet/capsule. De loperamide dient te blijven worden ingenomen tot 12 uur na het optreden van de laatste diarree. De loperamide mag niet langer dan 48 uur worden ingenomen.
- De patiënt dient na 24 uur diarree naast de loperamide te starten met Ciproxin®.
- Ter preventie hand-voet syndroom krijgt patiënt het advies om twee keer per dag de handen en voeten in te smeren.
- Zorg voor goede anticonceptie

ANTI-EMETICA BELEID
Stap 4: anti-emeticabeleid bij chemotherapie

WERKWIJZE
- Zie controlelijst
- Atropine 0,25 mg subcutaan toedienen voor irinotecan infusie. Zo nodig mag het tijdens infusie éénmaal herhaald worden.
- Het inlopen van oxaliplatin (in 120 min) wordt gecombineerd met eerst gelijktijdig de toediening van irinotecan (in 90 min) en daarna folinezuur (in 15 min). Hiervoor dienen wel alle middelen te zijn verdund in glucose 5% (toediening van oxaliplatin nooit combineren met NaCl0,9%).
- Op het infuus worden 2 chemolijnen aangesloten. De 1e lijn is voor de oxaliplatin en de 5-FU de 2 e lijn voor de irinotecan en de folinezuur.

- De toedienvolgorde is als volgt: Op lijn 1 start met de oxaliplatin in 120 minuten. Hierna de venflon of PICC / VAP naspoelen met 20ml NACL 0,9% en vervolgens de 5-FU zakken of cassette aansluiten. Op lijn 2 start met de irinotecan in 90 minuten, daarna de leucovorin in 15 minuten toedienen.
- De 46u lopende 5-FU wordt in 2 zakken aangeleverd of in 1 cassette.
- 5-FU 46 uur infuus kan ook via ambulant pompsysteem toegediend worden; via VAP / PICC en CADD-one pomp.
- De 5-FU voor de CADD pomp wordt standaard geleverd in 1 CADD-250ml-cassette met daarin de gehele dosis verdund in 200ml.

OPMERKINGEN
- Noodset (Atropine, 0,25 mg subcutaan) dient bij patiënt op kamer aanwezig te zijn voor het eventueel optreden van het acuut cholinergisch syndroom.
- Het infuus met irinotecan dient te worden beschermd tegen licht, dit geldt alleen voor de infuuszak, niet voor het systeem.
- Oxaliplatin wordt opgelost in een glucose 5% oplossing. **Niet mengen of gelijktijdig toedienen met zoutoplossingen of andere oplossingen die chloride bevatten.**
- Geen aluminium bevattende hulpmiddelen (bijvoorbeeld naalden) gebruiken, in verband met het risico op vorming van neerslag ondermeer bestaande uit platina.
- In verband met risico op duizeligheid mag patiënt 24 uur na toediening niet zelf autorijden.
- In combinatie met leucovorin ontstaat een potentiëring van de anti-tumor activiteit van 5-FU.
- Bij patiënten die gaan starten met 5-FU, tegafur of capecitabine vindt er bepaling plaats van de *DPYD* genotypering. *DPYD* is het gen dat codeert voor het enzym dihydropyrimidine dehydrogenase (DPD). Variaties in het gen *DPYD* kunnen leiden tot een verlaagde of afwezige enzymactiviteit. Fluorouracil wordt voor meer dan 80% door het enzym DPD omgezet in de inactieve metaboliet dihydrofluorouracil. Een lagere metabole activiteit van DPD leidt tot verhoogde intracellulaire concentraties van fluorodeoxyuridinemonofosfaat, de actieve metaboliet van fluorouracil en diens prodrug capecitabine. Hierdoor neemt het risico op bijwerkingen als neutropenie, trombopenie, hand-foot-syndroom en mucositis toe. In de Kaukasische populatie heeft ongeveer 3-5% een partiële DPD-deficiëntie en 0,1-0,2% een volledige DPD deficiëntie. In de Afrikaans-Amerikaanse populatie heeft ongeveer 8% een partiële DPD-deficiëntie.
- Voorafgaand aan irinotecan behandeling vindt *UGT1A1*-genotypering plaats. Bijwerkingen van irinotecan treden significant vaker op bij patiënten die homozygoot drager zijn van *UGT1A1**28, *UGT1A1**93, en *UGT1A1**6 doordat deze genvarianten tot verminderde glucuronidering en daarmee tot hogere concentraties van de actieve metaboliet SN-38 leiden.

EXCRETA
5 dagen besmet vanaf dag 1

BIJWERKINGEN
- beenmergdepressie (na ± 8 dagen)
- misselijkheid en braken
- diarree, late diarree (meestal rond vijfde dag)
- stomatitis / mucositis
- volledige haaruitval
- acuut cholinergisch syndroom (vroege diarree, buikpijn, conjunctivitis, rhinitis, hypotensie, vasodilatatie, transpiratie, rillingen, malaise, duizeligheid, visusstoornissen, tranenvloed en speekselvloed)

- korte termijn neurotoxiciteit; acute laryngopharyngeale dysesthesie (subjectief gevoel van dysfagie en dyspnoe zonder objectief bewijs voor ademhalingsmoeilijkheden. Syndroom, veelal uitgelokt of verergerd door koude, is binnen enkele minuten reversibel)
- lange termijn neurotoxiciteit ;sensorische perifere neuropathie, veelal uitgelokt of verergerd door koude. Incidentie en ernst neemt toe bij stijging cumulatieve dosis
- ontsteking of zwelling op de plaats van het infuus
- flebitis; vaak met bruine verkleuring van de huid ter plaatse
- obstipatie
- hand-voet syndroom (rode en pijnlijke huid)
- allergische huidreacties
- abnormale pigmentatie, acné
- oogtoxiciteit (droge of tranende ogen)
- leverfunctiestoornissen
- cardiotoxiciteit
- risico op infertiliteit

APPENDIX III: Toedienprotocol klassiek FOLFIRINOX (voor alle centra)

TOEDIENPROTOCOL / CONTROLELIJST FOLFIRINOX (klassiek)

	TIJD	PARAAF	VERPLK.HANDELINGEN	CONTROLES
Dag 1 0 uur			Controles Check inname anti-emetica en paracetamol 2 chemolijnen aansluiten met glucose 5%	RR: Pols: Temperatuur: Gewicht:
0 uur			Controles Toedienen atropine sc volgens afspraak Lijn 1: start oxaliplatin in 120 minuten Lijn 2: start Irinotecan in 90 minuten	extravasatie
+ 1 ½ uur			Controles Lijn 2: start folinezuur in 250ml glucose 5%in 15-30 minuten na de irinotecan	extravasatie
+2½ uur.			Start 5fu bolus gedurende 2-4 minuten nade oxaliplatin	
+ 2 ¾ uur			Controles Lijn 1: Start de 5FU gedurende 46uur, via infuus of CADD pomp Lijn 2: De venflon of PICC/VAP naspoelenmet 20ml NACL 0,9% Indien de 5-fu via de CADD pomp wordt toegediend in 46u mag de patiënt met ontslag Vervolg controlelijst is wanneer de 5-fu via de infuuspomp wordt toegediend, dan wordt deze in 2 zakken geleverd en deze moeten in 46u worden toegediend. Gelijktijdig meespoelen 2 liter gemengd/ 24u op een zijlijn met driewegkraan. (alleen bij een perifeer infuus noodzakelijk)	Controleer of de patiënt de tijd van aansluiten doorgeeft aan de thuiszorgorganisatie

Dag 2 +2 ½ uur			Controles Anti-emetica volgens beleid2e zak 5-FU aansluiten	Extravasatie RR: Pols: Temperatuur: Gewicht:
Dag 3 + 2 ½ uur			Controles Anti-emetica volgens beleid Einde 5-FU infuus	Extravasatie RR: Pols: Temperatuur: Gewicht:

BRONNEN

- Preopanc-2 studie. The (cost)effectiveness of neoadjuvant folfirinox versus neoadjuvant gemcitabine based chemoradiotherapy and adjuvant gemcitabine for (borderline) resectable pancreatic cancer . Dutch Pancreatic Cancer Group (DPCG). 24 april 2018
- C.L. Loprinzi, R.Qin, S.R. Dakhil, L. Fehrenbacher, K.A. Flynn, P. Atherton, D. Seisler, R. Qamar, G.C. Lewis, A. Grothey. (2013). Phase III Randomized, Placebo-Controlled, Double-Blind Study of Intravenous Calcium and Magnesium to Prevent Oxaliplatin-Induced Sensory Neurotoxicity (N08CB/Alliance). Journal of Clinical Oncology
- Conroy, T., et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. The New England Journal of Medicine .(2011) 346; 19: 1817-1825
- www.oncoline.nl – Oncolytica-interacties. KNMP Wetenschappelijk Instituut Nederlandse Apothekers, 2010 – Werkboek cytostatica. Vereniging van Integrale Kankercentra. 1997

APPENDIX IV: Toedienprotocol modified-FOLFIRINOX (voor alle centra)

TOEDIENPROTOCOL / CONTROLELIJST modified-FOLFIRINOX

	TIJD	PARAAF	VERPLK.HANDELINGEN	CONTROLES
Dag 1 0 uur			Controles Check inname anti-emetica en paracetamol 2 chemolijnen aansluiten met glucose 5%	RR: Pols: Temperatuur: Gewicht:
0 uur			Controles Toedienen atropine sc volgens afspraak Lijn 1: start oxaliplatin in 120 minuten Lijn 2: start Irinotecan in 90 minuten	extravasatie
+ 1 ½ uur			Controles Lijn 2: start folinezuur in 250ml glucose 5% in 15-30 minuten na de irinotecan	extravasatie
+ 2 ½ uur			Controles Lijn 1: Start de 5FU gedurende 46uur, via infuus of CADD pomp Lijn 2: De venflon of PICC/VAP naspoelenmet 20ml NACL 0,9% Indien de 5-fu via de CADD pomp wordt toegediend in 46u mag de patiënt met ontslag Vervolg controlelijst is wanneer de 5-fu via de infuuspomp wordt toegediend, dan wordt deze in 2 zakken geleverd en deze moeten in 46u worden toegediend. Gelijktijdig meespoelen 2 liter gemengd/ 24u op een zijlijn met driewegkraan. (alleen bij een perifeer infuus noodzakelijk)	Controleer of de patiënt de tijd van aansluiten doorgeeft aan de thuiszorgorganisatie

Dag 2 +2 ½ uur			Controles Anti-emetica volgens beleid2e zak 5-FU aansluiten	Extravasatie RR: Pols: Temperatuur: Gewicht:
Dag 3 + 2 ½ uur			Controles Anti-emetica volgens beleid Einde 5-FU infuus	Extravasatie RR: Pols: Temperatuur: Gewicht:

BRONNEN

- Preopanc-2 studie. The (cost)effectiveness of neoadjuvant folfirinox versus neoadjuvant gemcitabine based chemoradiotherapy and adjuvant gemcitabine for (borderline) resectable pancreatic cancer . Dutch Pancreatic Cancer Group (DPCG). 24 april 2018
- C.L. Loprinzi, R.Qin, S.R. Dakhil, L. Fehrenbacher, K.A. Flynn, P. Atherton, D. Seisler, R. Qamar, G.C. Lewis, A. Grothey. (2013). Phase III Randomized, Placebo-Controlled, Double-Blind Study of Intravenous Calcium and Magnesium to Prevent Oxaliplatin-Induced Sensory Neurotoxicity (N08CB/Alliance). Journal of Clinical Oncology
- Conroy, T., et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. The New England Journal of Medicine .(2011) 346; 19: 1817-1825
- www.oncoline.nl – Oncolytica-interacties. KNMP Wetenschappelijk Instituut Nederlandse Apothekers, 2010 – Werkboek cytostatica. Vereniging van Integrale Kankercentra. 1997
- Ozaka M, et al. Cancer Chemother Pharmacol 2018;81:1017.
- Conroy T, et al. J Clin Oncol 36, 2018 (suppl; abstr LBA4001). Abstract available online at https://meetinglibrary.asco.org/record/159164/abstract (Accessed on June 15, 2018).

APPENDIX V: DPWG RICTHLIJN

DPYD – 5-FU

Table 2 The translation of genotypes to predicted phenotypes, as gene activity scores

Patient genotype	Gene activity score
Carrier of no variants associated with either reduced functionality or fully dysfunctional DPD activity (*1/*1)	Gene activity score 2
Carrier of one variant associated with reduced functionality of DPD activity (*1/c.1236G>A or *1/c.2846A>T)	Gene activity score 1.5
Carrier of one variant associated with fully dysfunctional DPD activity (*1/*2A or *1/*13)	Gene activity score 1
Carrier of two variants associated with reduced functionality of DPD activity (for example c.1236G>A/c.2846A>T) Or Carrier of one variant associated with reduced functionality of DPD activity and one variant associated with fully dysfunctional DPD activity (combinations of c.2846A>T or c.1236G>A with *2A or *13, example given *2A/c.2846A>T)	PHENO: DPD enzyme activity cannot be predicted correctly, an additional phenotyping test is required to determine the DPD enzyme activity
Carrier of two variants associated with fully dysfunctional DPD activity (*2A/*2A or *13/*13 or *2A/*13)	Gene activity score 0

Wording from "Therapeutic Recommendations" section:

ALLELE/GENOTYPE/PHENOTYPE	DRUG	RECOMMENDATION
Activity Score 0	fluorouracil/capecitabine	Avoid systemic and cutaneous 5-fluorouracil or capecitabine
Activity Score 1 to 1.5	fluorouracil/capecitabine	Initiate therapy with 50% of the standard dose of fluorouracil or capecitabine. Further titration of the dose is possible, guided by toxicity.
Activity Score 0, 1 or 1.5	tegafur with uracil/gimeracil/DPD inhibitors	Avoid tegafur
Activity Score 2	fluorouracil/capecitabine/tegafur	No dose adaptation
Activity Score Unclear	fluorouracil/capecitabine	Determine the DPD activity (phenotyping) and adjust the initial dose based on available data

Reference

At the time this protocol was issued, the full DPWG guideline was available, at the following addresses:

Dutch Pharmacogenetics Working Group (DPWG) guideline for the gene–drug interaction of DPYD and fluoropyrimidines | European Journal of Human Genetics (nature.com)

Annotation of DPWG Guideline for capecitabine and DPYD (pharmgkb.org)

UGT1A1 – Irinotecan

Table: Genotype-phenotype translation

Genotype **Description**	**Examples**	**Phenotype predicted based on genotype**
two alleles with normal (or increased) enzyme activity	*1/*1, *1/*36	NM
***28 and one allele with normal (or increased) enzyme activity**	*1/*28, *28/*36	IM (*1/*28)
one allele with decreased enzyme activity other than *28 and one allele with normal (or increased) enzyme activity	*1/*6, *1/*37, *36/*37	IM other
two *28 alleles	*28/*28	PM (*28/*28)
two alleles with decreased enzyme activity, of which at least one is not *28	*6/*6, *6/*28, *28/*37	PM other

NM = Normal metaboliser, IM = intermediate metaboliser, PM = poor metaboliser

Table: Summary therapeutic recommendations based on *UGT1A1* predicted phenotype for irinotecan

***UGT1A1* predicted phenotype**	**Therapeutic recommendation**
PM (*28/*28)	Start with 70% of the normal dose[a]. If the patient tolerates this initial dose, the dose can be increased, guided by the neutrophil count.
PM other	Start with 70% of the normal dose[a]. If the patient tolerates this initial dose, the dose can be increased, guided by the neutrophil count.
IM (*1/*28)	No action required
IM other	No action required

IM = intermediate metaboliser, PM = poor metaboliser

[a] The normal dose is defined as the dose the patient would receive if he/she would not have a gene variant.

Reference

At the time this protocol was issued, the full DPWG guideline was available, at the following addresses:

Dutch pharmacogenetics working group (DPWG) guideline for the gene–drug interaction between UGT1A1 and irinotecan | European Journal of Human Genetics (nature.com)

Annotation of DPWG Guideline for irinotecan and UGT1A1 (pharmgkb.org)

APPENDIX VI: KINETIEKLIJSTEN

KINETIEKLIJST – FOLFIRINOX MET 5-FU bolus **KUURCYCLUS 1**

Studienummer patiënt: _____

Datum kuur: ___ / ___ / ___

	VERPLK.HANDELINGEN	GEPLANDE TIJD	WERKELIJKE TIJD	OPMERKINGEN/CONTROLES	PARAAF
Dag 1 **00:00**	**Controles** 2 chemolijnen aansluiten met glucose 5% Plaats een Venflon naald voor bloedafname in de arm waarin GEEN chemo inloopt				
00:00	**Bloedafname baseline** **DHU/DHU: 1x 4 ml bloed EDTA, paars**				
00:00	**Bloedafname baseline** **ctDNA: 1x 10 ml bloed EDTA, paars**				
00:05	Lumen 1: start oxaliplatin Lumen 2: start Irinotecan		Oxaliplatin Start: Eind: Irinotecan Start: Eind:	Oxaliplatin Dosis: Inlooptijd: Irinotecan Dosis: Inlooptijd:	
01:35	Lumen 2: spoelen lijn met glucose 5% en start folinezuur in glucose 5% na de irinotecan				
02:15	Lumen 1 en 2: lijn na folinezuur en oxaliplatin naspoelen				
02:30	Lumen 1: Start 5FU bolus in gedurende 2-4 minuten		5-FU Bolus Start: Eind:	5-FU bolus Dosis: Inlooptijd Bolus:	
02:35	Lumen 1: spoelen lijn na bolus				
02:40	**Bloedafname t= na einde bolus** **Irinotecan: 1x 4 ml bloed lithium heparine**				
02:40	**Bloedafname t= na einde bolus** **Oxaliplatin: 1x 4 ml bloed lithium heparine**				
02:40	**Bloedafname t= na einde bolus** **5-FU: 1x 4 ml bloed EDTA, paars**			Gimeracil toegevoegd: Ja/Nee	

				Tijdstip:	
02:45	Lumen 1: Start de 5FU gedurende 46uur, via infuus of CADD pomp of elastomeerpomp		5-FU continu Start: Eind:	5-FU continu Dosis: 5-FU continu inlooptijd:	
03:15	**Bloedafname t=30 min** **5-FU: 1x 4 ml bloed EDTA, paars**			Gimeracil toegevoegd: Ja/Nee Tijdstip:	
03:45	**Bloedafname t=1 uur** **5-FU: 1x 4 ml bloed EDTA, paars**			Gimeracil toegevoegd: Ja/Nee Tijdstip:	
04:15	**Bloedafname t =1.5 uur** **5-FU: 1x 4 ml bloed EDTA, paars**			Gimeracil toegevoegd: Ja/Nee Tijdstip:	
04:45	**Vingerprik t=2 uur** **5-FU: DBS Whatman-kaart: 2 druppels** **5-FU: DBS HemaXis-kaart: 2 druppels**			Uitgevoerd door: VPK/OND/PT	
04:45	**Bloedafname t=2 uur** **5-FU: 1x 4 ml bloed EDTA, paars**			Gimeracil toegevoegd: Ja/Nee Tijdstip:	
04:50	Indien de 5-FU via de CADD/elastomeer pomp wordt toegediend in 46u mag de patiënt met ontslag.			Type pomp: CADD / elastomeer / infuus	
Dag 3 ***1-4 uur vóór einde 5-FU cassette*** **00:00**	**Bloedafname t=dag 3** **Irinotecan: 1x 4 ml bloed lithium heparine**				
00:00	**Bloedafname t=dag 3** **5-FU: 1x 4 ml bloed EDTA, paars**			Loopt 5-FU continu nog? Ja/Nee Gimeracil toegevoegd: Ja/Nee Tijdstip:	
00:01	**Vingerprik t=dag 3** **5-FU: DBS Whatman-kaart: 2 druppels** **5-FU: DBS HemaXis-kaart: 2 druppels**			Uitgevoerd door: VPK/OND/PT	
Einde 5-FU cassette/infuus	Verwijderen lijn/afkoppelen pomp en flushen PAC		Eind 5-FU continu:	Evt. Restvolume pomp:	

KINETIEKLIJST – FOLFIRINOX MET 5-FU bolus **KUURCYCLUS 2**

Studienummer patiënt: _____

Datum kuur: ___ / ___ / ___

	VERPLK.HANDELINGEN	**GEPLANDE TIJD**	**WERKELIJKE TIJD**	**OPMERKINGEN/CONTROLES**	**PARAAF**
Dag 1 **00:00**	**Controles** 2 chemolijnen aansluiten met glucose 5% Plaats een Venflon naald voor bloedafname in de arm waarin GEEN chemo inloopt				
00:05	Lumen 1: start oxaliplatin Lumen 2: start Irinotecan		Oxaliplatin Start: Eind: Irinotecan Start: Eind:	Oxaliplatin Dosis: Inlooptijd: Irinotecan Dosis: Inlooptijd:	
01:35	Lumen 2: spoelen lijn met glucose 5% en start folinezuur in glucose 5% na de irinotecan				
02:15	Lumen 1 en 2: lijn na folinezuur en oxaliplatin naspoelen				
02:30	Lumen 1: Start 5FU bolus in gedurende 2-4 minuten		5-FU Bolus Start: Eind:	5-FU bolus Dosis: Inlooptijd Bolus:	
02:35	Lumen 1: spoelen lijn na bolus				
02:40	**Bloedafname t= na einde bolus** **Irinotecan: 1x 4 ml bloed lithium heparine**				
02:40	**Bloedafname t= na einde bolus** **Oxaliplatin: 1x 4 ml bloed lithium heparine**				
02:40	**Bloedafname t= na einde bolus** **5-FU: 1x 4 ml bloed EDTA, paars**			Gimeracil toegevoegd: Ja/Nee Tijdstip:	
02:45	Lumen 1: Start de 5FU gedurende 46uur, via infuus of CADD pomp of elastomeerpomp		5-FU continu Start: Eind:	5-FU continu Dosis: 5-FU continu inlooptijd:	
04:45	**Vingerprik t=2 uur** **5-FU: DBS Whatman-kaart: 2 druppels** **5-FU: DBS HemaXis-kaart: 2 druppels**			Uitgevoerd door: VPK/OND/PT	

04:45	**Bloedafname t=2 uur** **5-FU: 1x 4 ml bloed EDTA, paars**			Gimeracil toegevoegd: Ja/Nee Tijdstip:	
04:50	Indien de 5-FU via de CADD/elastomeer pomp wordt toegediend in 46u mag de patiënt met ontslag.			Type pomp: CADD / elastomeer / infuus	
<u>Dag 3</u> ***1-4 uur vóór einde 5-FU cassette*** **00:00**	**Bloedafname t=dag 3** **Irinotecan: 1x 4 ml bloed lithium heparine**				
00:00	**Bloedafname t=dag 3** **5-FU: 1x 4 ml bloed EDTA, paars**			Loopt 5-FU continu nog? Ja/Nee Gimeracil toegevoegd: Ja/Nee Tijdstip:	
00:01	**Vingerprik t=dag 3** **5-FU: DBS Whatman-kaart: 2 druppels** **5-FU: DBS HemaXis-kaart: 2 druppels**			Uitgevoerd door: VPK/OND/PT	
Einde 5-FU cassette/infuus	Verwijderen lijn/afkoppelen pomp en flushen PAC		Eind 5-FU continu:	Evt. Restvolume pomp:	

KINETIEKLIJST – FOLFIRINOX ZONDER 5-FU bolus KUURCYCLUS 1

Studienummer patiënt: _____

Datum kuur: ___ / ___ / ___

	VERPLK.HANDELINGEN	GEPLANDE TIJD	WERKELIJKE TIJD	OPMERKINGEN/CONTROLES	PARAAF
Dag 1 **00:00**	**Controles** 2 chemolijnen aansluiten met glucose 5% Plaats een Venflon naald voor bloedafname in de arm waarin GEEN chemo inloopt				
00:00	**Bloedafname baseline** **DHU/DHU: 1x 4 ml bloed EDTA, paars**				
00:00	**Bloedafname baseline** **ctDNA: 1x 10 ml bloed EDTA, paars**				
00:05	Lumen 1: start oxaliplatin Lumen 2: start Irinotecan		Oxaliplatin Start: Eind: Irinotecan Start: Eind:	Oxaliplatin Dosis: Inlooptijd: Irinotecan Dosis: Inlooptijd:	
01:35	Lumen 2: spoelen lijn met glucose 5% en start folinezuur in glucose 5% na de irinotecan				
02:15	Lumen 1 en 2: lijn na folinezuur en oxaliplatin naspoelen				
02:30	Lumen 1: Start de 5FU gedurende 46uur, via infuus of CADD pomp of elastomeerpomp		5-FU continu Start: Eind:	5-FU continu Dosis: 5-FU continu inlooptijd:	
03:00	**Bloedafname t= 30 min** **Irinotecan: 1x 4 ml bloed lithium heparine**				
03:00	**Bloedafname t= 30 min** **Oxaliplatin: 1x 4 ml bloed lithium heparine**				
03:00	**Bloedafname t=30 min** **5-FU: 1x 4 ml bloed EDTA, paars**			Gimeracil toegevoegd: Ja/Nee Tijdstip:	

03:30	**Bloedafname t=1 uur** **5-FU: 1x 4 ml bloed EDTA, paars**			Gimeracil toegevoegd: Ja/Nee Tijdstip:	
04:00	**Bloedafname t =1.5 uur** **5-FU: 1x 4 ml bloed EDTA, paars**			Gimeracil toegevoegd: Ja/Nee Tijdstip:	
04:30	**Vingerprik t=2 uur** **5-FU: DBS Whatman-kaart: 2 druppels** **5-FU: DBS HemaXis-kaart: 2 druppels**			Uitgevoerd door: VPK/OND/PT	
04:30	**Bloedafname t=2 uur** **5-FU: 1x 4 ml bloed EDTA, paars**			Gimeracil toegevoegd: Ja/Nee Tijdstip:	
04:35	Indien de 5-FU via de CADD/elastomeer pomp wordt toegediend in 46u mag de patiënt met ontslag.			Type pomp: CADD / elastomeer / infuus	
<u>Dag 3</u> ***1-4 uur vóór einde 5-FU cassette*** **00:00**	**Bloedafname t=dag 3** **Irinotecan: 1x 4 ml bloed lithium heparine**				
00:00	**Bloedafname t=dag 3** **5-FU: 1x 4 ml bloed EDTA, paars**			Loopt 5-FU continu nog? Ja/Nee Gimeracil toegevoegd: Ja/Nee Tijdstip:	
00:01	**Vingerprik t=dag 3** **5-FU: DBS Whatman-kaart: 2 druppels** **5-FU: DBS HemaXis-kaart: 2 druppels**			Uitgevoerd door: VPK/OND/PT	
Einde 5-FU cassette/infuus	Verwijderen lijn/afkoppelen pomp en flushen PAC		Eind 5-FU continu:	Evt. Restvolume pomp:	

KINETIEKLIJST – FOLFIRINOX <u>ZONDER</u> 5-FU bolus KUURCYCLUS 2

Studienummer patiënt: _____

Datum kuur: ___ / ___ / ___

	VERPLK.HANDELINGEN	GEPLANDE TIJD	WERKELIJKE TIJD	OPMERKINGEN/CONTROLES	PARAAF
<u>Dag 1</u> **00:00**	**Controles** 2 chemolijnen aansluiten met glucose 5% Plaats een Venflon naald voor bloedafname in de arm waarin GEEN chemo inloopt				
00:05	Lumen 1: start oxaliplatin Lumen 2: start Irinotecan		<u>Oxaliplatin</u> Start: Eind: <u>Irinotecan</u> Start: Eind:	<u>Oxaliplatin</u> Dosis: Inlooptijd: <u>Irinotecan</u> Dosis: Inlooptijd:	
01:35	Lumen 2: spoelen lijn met glucose 5% en start folinezuur in glucose 5% na de irinotecan				
02:15	Lumen 1 en 2: lijn na folinezuur en oxaliplatin naspoelen				
02:30	Lumen 1: Start de 5FU gedurende 46uur, via infuus of CADD pomp of elastomeerpomp		<u>5-FU continu</u> Start: Eind:	5-FU continu Dosis: 5-FU continu inlooptijd:	
03:00	**Bloedafname t= 30 min** **Irinotecan: 1x 4 ml bloed lithium heparine**				
03:00	**Bloedafname t= 30 min** **Oxaliplatin: 1x 4 ml bloed lithium heparine**				
03:00	**Bloedafname t=30 min** **5-FU: 1x 4 ml bloed EDTA, paars**			Gimeracil toegevoegd: Ja/Nee Tijdstip:	
04:30	**Vingerprik t=2 uur** **5-FU: DBS Whatman-kaart: 2 druppels** **5-FU: DBS HemaXis-kaart: 2 druppels**			Uitgevoerd door: VPK/OND/PT	

04:30	**Bloedafname t=2 uur** **5-FU: 1x 4 ml bloed EDTA, paars**			Gimeracil toegevoegd: Ja/Nee Tijdstip:	
04:35	Indien de 5-FU via de CADD/elastomeer pomp wordt toegediend in 46u mag de patiënt met ontslag.			Type pomp: CADD / elastomeer / infuus	
<u>Dag 3</u> ***1-4 uur vóór einde 5-FU cassette*** **00:00**	**Bloedafname t=dag 3** **Irinotecan: 1x 4 ml bloed lithium heparine**				
00:00	**Bloedafname t=dag 3** **5-FU: 1x 4 ml bloed EDTA, paars**			Loopt 5-FU continu nog? Ja/Nee Gimeracil toegevoegd: Ja/Nee Tijdstip:	
00:01	**Vingerprik t=dag 3** **5-FU: DBS Whatman-kaart: 2 druppels** **5-FU: DBS HemaXis-kaart: 2 druppels**			Uitgevoerd door: VPK/OND/PT	
Einde 5-FU cassette/infuus	Verwijderen lijn/afkoppelen pomp en flushen PAC		Eind 5-FU continu:	Evt. Restvolume pomp:	

APPENDIX VII: CTCAE

In the present study, adverse events and/or adverse drug reactions will be recorded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 (November 27, 2017).

At the time this protocol was issued, the full CTC document was available on the NCI website, at the following address: Common Terminology Criteria for Adverse Events (CTCAE) (cancer.gov)

APPENDIX VIII: Suggested Decision Tree – Model Informed Precision Dosing of 5-FU

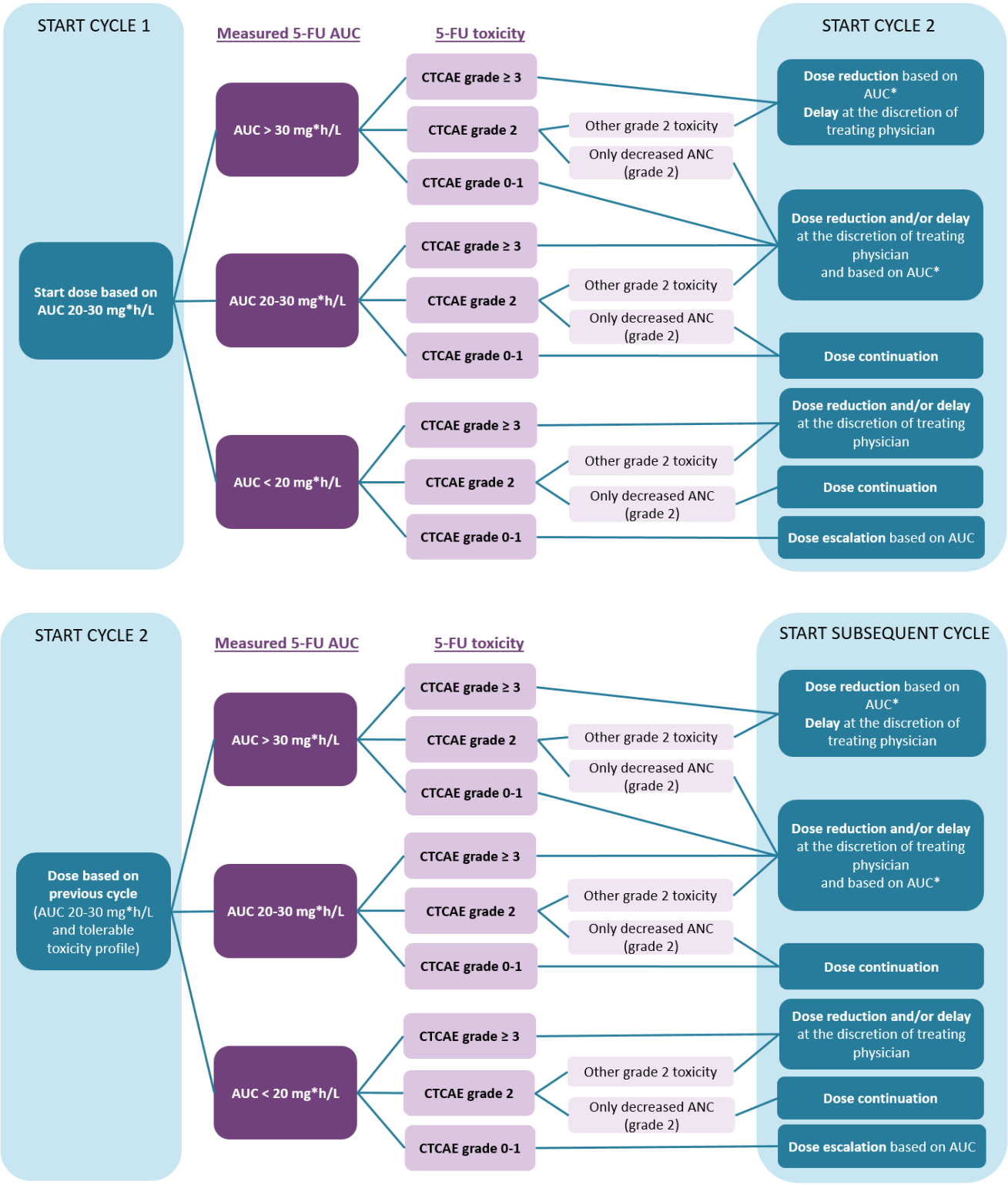


Figure 11: Suggested model-informed precision dosing and toxicity-guided dosing nomogram for patients treated with 5-FU (for PART B)

*In case of grade ≥ 2 toxicity and an $AUC_{0\text{-}46h}$ ≤ 30 mg*h/L, AUC-based dosing may be used for guiding dose reductions. If feasible/tolerable, the minimum 5-FU dose to achieve AUC ≥ 20 mg*h/L should be considered for 5-FU efficacy.

APPENDIX IX: COMPLETE LIST OF PERFUPANC INVESTIGATORS

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