STUDY PROTOCOL – PROTOCOL FOR ETHICAL APPROVAL ITALY

The ADAPTA Study: **AD**juvant chemother**AP**y after curative intent resec**T**ion of **A**mpullary cancer. A pan-European prospective multicenter double single arm cohort study.	
Abbreviation title: ADAPTA	
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Promotor:	**Fondazione Poliambulanza**
Coordination center	**U.O.**
Principle investigator	***Fondazione Poliambulanza, Brescia, Italy*** *Professor Mohammed Abu Hilal* *Department of Surgery* *Tel: +39 375 632 6711* *Email: abuhilal9@gmail.com* *Dr. Alberto Zaniboni* *Department of Medical Oncology* Email: zanibonialbert@gmail.com
CO-investigators	***Fondazione Poliambulanza, Brescia, Italy*** *Mr. D.H.L Lemmers* *Department of Surgery* *Tel: +31-645425610*

	Email: d.h.lemmers@amsterdamumc.nl *Mr. B.A. Uijterwijk* *Department of Surgery* *Tel: +31-640380827* *Email: Bas.uijterwijk@poliambulanza.it*

INTRODUCTION

Background and Rationale

The incidence of ampullary adenocarcinoma (AAC) resembles 0.2% to 0.5% of all gastro-intestinal cancers and 7% of all periampullary cancers [1,2]. The five-year overall survival (OS) varies between 30% and 70%. This wide range could be explained by the morphological heterogeneity of the three known subtypes of AAC consisting of the intestinal type, the pancreatobiliary (PB) type, and a mixed subtype. It is believed that the PB subtype has the most aggressive biological behavior [3,4]. To date there have been no prospective cohort studies evaluating the effect of adjuvant chemotherapy after curative intent resection of AAC designed to look at specific histological subtypes. Some studies suggest a benefit of adjuvant chemo-radiotherapy with 5-fluorouracil (5-FU), but to date no randomized trials confirm a survival improvement [21-24]. Adjuvant chemotherapy was studied in the international ESPAC-3 trial [25]. In this study 427 patients were included of which 297 had AAC. Patients were randomized to observation or adjuvant chemotherapy, with either gemcitabine or 5-FU. When the analysis was restricted to patients with AAC, those treated with gemcitabine had a median survival of 71 months versus 41 months in the observation alone group. The median survival in the 5-FU group was 57.8 months. There were no statistically significant differences in survival between ampullary subtypes. At the start of this trial, classification of AAC was not being widely applied and eighty ampullary tumors were classified as intestinal, 46 as PB, 9 as mixed, and 162 as indeterminate, which might be an explanation for finding no statistically significant outcomes. A recent retrospective study including 214 patients with resected AAC [26] demonstrated that only patients with the PB and mixed subtypes benefit from adjuvant therapy with an improved median overall survival of 85 months vs. 65 months for no adjuvant therapy, p = 0.005. For patients with the intestinal subtype, there was no benefit from adjuvant chemotherapy. A retrospective study of our own research group [9] demonstrated comparable results. This study included 887 patients with resected AAC. Adjuvant chemotherapy independently predicted an improved OS in the PB subtype (HR = 0.61 [0.40– 0.93]) and not in the intestinal subtype [9].

Thus, although there is evidence of survival improvement of adjuvant treatment for ACC, this has to be proven in prospective studies. As described in literature, the PB and mixed subtype have the worst 5-year

OS (22% to 44%) and have the most aggressive biological behavior. In addition, the PB subtype resembles pancreatic adenocarcinoma. For pancreatic cancer, the 5-fluorouracil, irinotecan, oxaliplatin and leucovorin (FOLFIRINOX) regimen led to a significant longer survival compared to gemcitabine in patients with resected pancreatic cancer [27]. A phase II study by Overmann et al. [28] showed that the combination of Capecitabine and Oxaliplatin (CAPOX) is administered in patients with a good performance status was well tolerated and resulted in a superior response rate and longer OS compared with other regimens in patients with AAC (all subtypes) and duodenal cancer.

Although retrospective research has shown beneficiary effect of adjuvant gemcitabine in the PB and MT subtype of AAC, no favorable effect in the intestinal subgroup has been observed. Intestinal subtype AAC has great resemblance with colonic and duodenal cancer, therefore we hypothesize that patients with intestinal subtype AAC will benefit from adjuvant treatment with CAPOX. Since FOLFIRINOX currently is the preferred adjuvant treatment instead of gemcitabine in pancreatic cancer, patients with the PB and mixed subtype might benefit from adjuvant treatment with FOLFIRINOX. In this prospective cohort study, we will investigate whether this adjuvant treatment strategy based on the histopathological subtypes of AAC will result in improved survival. In addition, we will conduct molecular sub-studies in the histopathological subtypes of AAC to gain more knowledge on the biological behavior of this rare disease.

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STUDY DESIGN

This study is a pan-European prospective multicenter observational cohort study. Eligible patients are after a curative resection of an AAC, have a good performance score of 0 or 1 and are expected to start adjuvant chemotherapy. All patients after curative resection of an AAC will be asked to participate in the study. Inclusion will take place after resection and central histopathological review of the resected specimen by a team of dedicated Hepato-pancreato-biliary pathologists of the participating center. Final diagnosis of PB/mixed or intestinal subtype will be reached by consensus based on morphological and

immunohistochemical characteristics. The primary endpoint is 3-year disease-free survival. In total we will include 200 patients, 100 with the PB and mixed subtype, and 100 with the intestinal subtype.
After pancreatoduodenectomy, 8 cycles of systemic FOLFIRINOX or CAPOX will be administered. Adjuvant therapy should be started within 8 weeks after surgery. The follow up period is until recurrence of disease/ death or five years after randomization. The statistical analysis will take place 1.5 years after last inclusion.

OBJECTIVES

The primary objective of this prospective cohort study is to evaluate the efficacy of adjuvant CAPOX (in the intestinal subgroup of AAC after complete resection), and FOLFIRINOX (in the PB and mixed subgroup of AAC after complete resection) in terms of disease-free survival at 3-years.
Secondary objectives include 5-year disease free survival, 5-year overall survival, safety and tolerability of treatment, delivered dose intensity, quality of life, patient-reported outcomes, patterns of disease recurrence, locoregional control, and molecular subtyping of AAC in relation to survival and recurrence. Results will be compared with literature finding (basically based on retrospective studies) in order to validate and eventually confirm the literature evidences regarding the AAC subtypes.

STUDY POPULATION

Eligible patients have (borderline) resectable non-metastatic AAC. Resectability is determined on preoperative imaging and defined by the Dutch Pancreatic Cancer Group definitions for resectability of pancreatic adenocarcinoma (DPCG, 2012, Table 1) Resectable disease is defined as no arterial (hepatic artery, superior mesenteric artery, or coeliac trunk) tumor contact and venous (portal vein or superior mesenteric vein) tumor contact of 90 degrees or less. Borderline resectable disease is defined as arterial tumor contact 90 degrees or less and venous contact of 90 to 270 degrees without occlusion. The

diagnosis of ampullary cancer must be confirmed by pathological evaluation of the resection specimen or a tumor biopsy/fine needle aspiration. Patients should have a good performance score of 0 or 1 (Table 2).

Table 1 Dutch Pancreatic cancer group definitions for resectability of pancreatic adenocarcinoma				
	SMA	Celiac axis	CHA	SMV-PV
Resectable (all 4 required)	No contact	No contact	No contact	≤90° contact
Borderline resectable (minimally one required)	≤90° contact	≤90° contact	≤90° contact	≤90°-270° contact and no occlusion
Irresectable (minimally one required)	Contact >90°	Contact >90°	Contact >90°	Contact >270° or occlusion
SMA superior mesenteric artery, CHA common hepatic artery, SMV superior mesenteric artery, PV portal vein				

Table 2.

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

INCLUSION CRITERIA

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

- Adult patients with histologically or cytologically confirmed AAC with subtyping of pancreatobiliary/mixed subtype or intestinal subtype
- After curative resection for ampullary cancer without metastatic disease.
- WHO performance status 0 or 1
- Able and willing to receive adjuvant chemotherapy
- R0/ R1 resection
- Age ≥ 18 years
- Written informed consent
- DPYD mutation tested [REF. 29]
- UGT1A mutation tested [REF. 29]
- CTCAE graded [REF. 30]

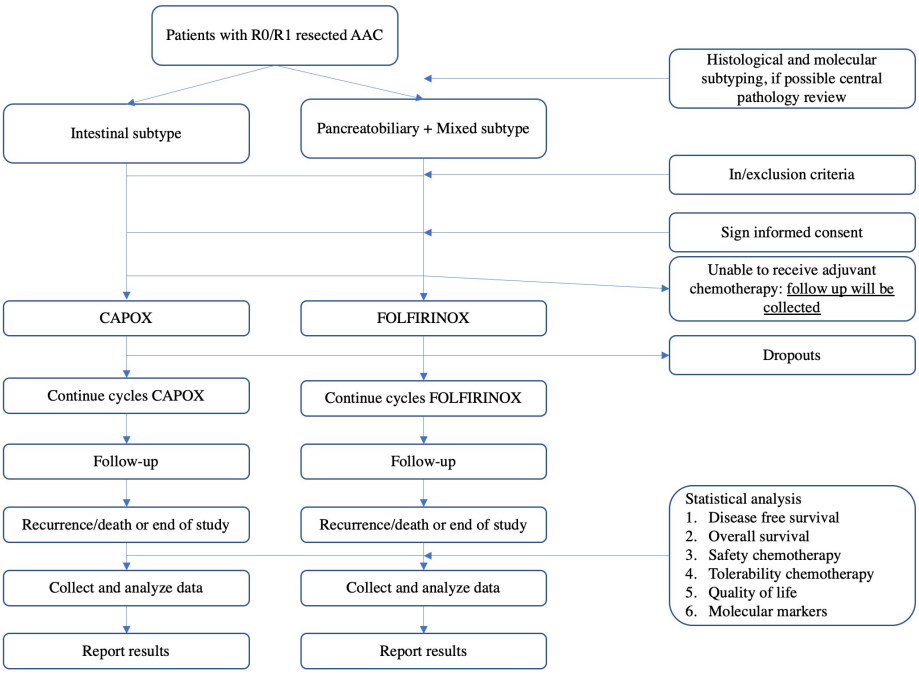
EXCLUSION CRITERIA

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

- Prior radiotherapy, chemotherapy, or resection for AAC.
- Previous malignancy (excluding non-melanoma skin cancer), unless no evidence of disease and diagnosed more than 5 years before diagnosis of AAC.
- Pregnancy.
- R2 resection.
- Adjuvant chemotherapy started more than 12 weeks after surgery (aim to start within 8 weeks)
- Serious concomitant systemic disorders that would compromise the safety of the patient or his/her ability to complete the study, at the discretion of the investigator.
- Known hypersensitivity or contraindications against capecitabine, 5 FU, Irinotecan, or Oxaliplatin
- Inadequate organ functions, characterized by:
    - Leucocytes (WBC) < 3.0 X 109/l
    - Neutrophils < 1.500 (count per microliter of blood)
    - Platelets < 100 x 109 /l

- Hemoglobin < 8 mmol/l
- Renal function: E-GFR < 50 ml/min (serum creatinine < 1.5 x UNL)
- cholestasis with elevated levels of bilirubin and/or alkaline phosphatase > 3x UNL (can be improved by biliary drainage if necessary)
- elevated transaminases (ALAT/ASAT) ≥ 5 x UNL
- hypoalbuminemia < 2.5 g/dl
- Inadequate coagulation status INR > 2 or Quick < 50%, aPTT >50 sec in the absence of any drugs interfering with coagulation such as acenocoumarin, warfarin, phenprocoumon, NMH or UFH.

STUDY DESIGN FLOWCHART



TREATMENT OF SUBJECTS

Treatment

This study focusses on patients after curative intent resection for AAC. Patients will be included after post-operative pathology report confirms an adenocarcinoma of the ampulla of Vater. The adjuvant chemotherapy will be started when the patient is recovered, aiming within 8 weeks from surgery.

Patients operated with palliative intent or treated with palliative chemotherapy are not eligible for the ADAPTA study. Patients are eligible for a surgical exploration if they have non-metastatic (borderline) resectable disease on imaging. Surgery starts with a staging laparoscopy. During the same surgical procedure, a resection will be performed when no metastatic or locally advanced (unresectable) disease is found. Patients with distant metastasis or locally advanced disease at staging or surgery will continue with standard palliative care according to the national or local guideline for AAC and will be therefore unable to participate in this study.

The adjuvant chemotherapy involves eight cycles of FOLFIRINOX/CAPOX. Cycles are repeated every 3 weeks for CAPOX and every 2 weeks for FOLFIRINOX. the FOLFIRINOX regimen is based on the regimen of the phase III trial (ACCORD/PRODIGE trial) for metastatic pancreatic cancer. This trial follows the modified FOLFERINOX treatment described in [27]. mFOLFIRINOX is a dosed reduces version which can be used in standard practice, such as normal FOLFIRINOX:

mFolfirinox:

- Oxaliplatin (Eloxatin®) 85 mg/m² D1 over 2 hours, followed by
- Irinotecan (Campto®) 150 mg/m² D1 over 90 minutes to begin 30 min.
  After the Folinic acid infusion is started. Folinic acid 400 mg/m² (racemic mixture) (or 200 mg/m² if L-folinic acid is used), IV infusion over 2 hours. 5-FU 2.4 g/m² IV continuous infusion over 46 hours (1200 mg/m²/ day). TREATMENT DURATION: 16 weeks

The mFOLFIRINOX regimen is described in the table below:

Day	Drug	Dose	Route	Diluent & Rate
Day 1	Oxaliplatin	85mg/m2	IV in 2h	
Immediately followed	Leucovorin (folinic acid)	400mg/m2	IV 2h	

After 30 minutes	Irinotecan	150mg/m2	IV 1h	Over 90 minutes to begin 30 min after folinic acid infusion is started
followed	5Fluorouracil	2400mg/m2	IV in 48h	

The CAPOX regimen is described in the table below:

Day	Drug	Dose	Route	Diluent & Rate
Day 1	Oxaliplatin	130mg/m2	IV Infusion	500mls Glucose 5% over 2 hours
Days 1-14	Capecitabine	1000mg/m2	Twice a day Oral	

Escape medication in case of acute toxicity

Acute toxicity treatment for FOLFIRINOX/CAPOX:

Indication	**Medication**
Cholinergic symptoms (early diarrhea)	Prophylactic atropine may be considered in patients experiencing cholinergic symptoms
Diarrhea abdominal cramp = diarrhea may be severe and delayed with irinotecan	Loperamide 4 mg at the onset of diarrhea, then 2 mg every two hours once first liquid stool appears and continue until 12 hours after the last liquid stool. Do not use for longer than 48 hours.
Nausea and vomiting	Anti-emetics

Guidelines for dose adjustment of FOLFIRINOX/CAPOX are reported in Appendix.

Standard pre-medication

Patients will receive co-medication as proposed below or according to standard procedures of local site.

Administered 30-60 minutes prior to adjuvant FOLFIRINOX/CAPOX chemotherapy:

- Dexamethasone 8mg IV bolus over 3-5 minutes or PO
- Ondansetron 8mg IV bolus over 3-5 minutes or PO
- Atropine 0.25 mg SC 5 minutes before start of Irinotecan
- Glucose 5%flush should be administered before and after Oxaliplatin

METHODS

Primary Endpoint

3-year Disease Free Survival (DFS), defined as survival without locoregional progressive disease, the occurrence of distant metastases, the occurrence of second or recurrent Ampullary cancer from the date of study participation. Death from any cause is also considered an event for this endpoint. Patients alive and free of all these events will be censored at the last follow-up.

Secondary Endpoint

Secondary objectives include 5-year disease-free survival, 5-year overall survival, safety and tolerability of treatment, delivered dose intensity, quality of life, patterns of disease recurrence, locoregional control, and molecular markers of AAC.

In addition, the analysis of the molecular markers through the genetic test of tumor samples will be performed (substudy).

Study Procedure

Eligible patients are informed about the study and written informed consent is required prior to inclusion. Study-specific assessments and evaluations will be performed after written informed consent is obtained for permission to prospectively observe the patients, send questionnaires, use peri-operative data and medical history anonymously. Within the informed consent there will be an advice to avoid pregnancy during chemotherapy

Patients will be included after surgery when post-operative pathology examination is complete. Therefore, the following information will be collected retrospectively after informed consent:

- Medical history and physical exam.
- Laboratory tests: hemoglobin, WBC, differential count, platelets, bilirubin, ALAT, ASAT, Alkaline Phosphatase, gamma-GT, creatinine, albumin, glucose, CRP, PTT.
- Testing of the DPYD gene[29]
- Testing of the UGT1A gene[29]
- CT-scan of chest and abdomen, following CT protocol as described by Dutch Radiology Association (NVvR): max. 3 mm slices; 150 cc contrast at 4-5 cc/s (18 G i.v. catheter); Pancreas parenchyma phase preferably 15-30 sec after bolus tracking, otherwise 35-45 sec p.i.; Porto-venous phase 70 sec p.i. or 45-44 sec after bolustracking.25
- Endoscopic ultrasonography (EUS) with Fine Needle Aspiration or Biopsy (FNA or FNB) when performed. To obtain a cytological/histological diagnosis most patients will undergo EUS with FNA/FNB. A maximum of 2 EUS with FNA/FNB attempts in the pancreatic cancer center is allowed.
- Biliary stenting when necessary. Required in patients with obstructive jaundice (defined as bilirubin > 1.5 times normal, which in clinical practice frequently translates to a cut-off value of 25µmol/L).

Patients will be included after surgery when post-operative pathology examination is complete. Therefore, the following information will be collected retrospectively after informed consent:

- Physical exam.
- Laboratory tests: hemoglobin, WBC, platelets, bilirubin, ALAT, ASAT, alkaline phosphatase, gamma-GT, creatinine, albumin, glucose, PTT.
- Pancreatic resection (open or minimally-invasive; minimally-invasive resection only by surgeons with experience of at least 50 minimally-invasive resections and at least 20 per year).
- Postoperative complication within 90 days (Clavien-Dindo classification).
- Tumor markers CA 19-9 and CEA, at time of follow-up imaging.
- Serum (maximum of 40cc) for biomarkers including ctDNA, miRNA, glycomics, proteomics and TEPs just before surgery and within 45 days after surgery (before start adjuvant chemotherapy).

A standardized histopathology protocol will be developed by pathologist from expert pancreatic centers participating in the trial for the pathological evaluation of the resection specimen. A team of dedicated

pathologist will be formed to reach consensus over every case included in the ADAPTA trial. After reaching consensus, cases will be included either in the Intestinal subgroup, or in the PB+Mixed subtype group and the adjuvant CAPOX (in intestina group) or adjuvant FOLFIRINOX (in PB+mixed group) will be administrated.

The treatment of FOLFIRINOX, and CAPOX are registered for the treatment of pancreatic cancer and duodenal/ colon cancer respectively. We classified this study as low risk, there is only a slight chance of moderate damage.

STATISTICAL ANALYSIS

Primary endpoint analysis

The endpoint for the primary analysis is 3-year Disease Free Survival (DFS). The formal test for difference in DFS between the two treatment arms will be performed with a multivariable Cox regression analysis with adjustment for the stratification factors (resectable versus borderline resectable, and institution). Additional post-hoc adjustment is performed for confounding factors that are not equally distributed across treatment arms due to chance. The actuarial method of Kaplan-Meier will be used to estimate DFS probabilities at appropriate time points, while the Greenwood estimate will be used to construct corresponding 95% confidence intervals (CIs). Kaplan-Meier curves will be generated to illustrate DFS, for all patients as well as per treatment arm individual. We will also retrospectively propensity score match all included patients with the retrospective registry of the ISGACA consortium to evaluate if there is a difference in DFS between patients without adjuvant FOLFIRINOX/CAPOX and patients enrolled in the ADAPTA trial.

Secondary endpoints analysis

- Chemotherapy rate will be compared using Fisher's exact test.
- 5-year disease free survival will be compared with a multivariable Cox regression analysis
- 5-year overall survival will be compared with a multivariable Cox regression analysis

- 3-year overall survival will be compared with a multivariable Cox regression analysis
- Chemotherapy completion rate will be compared using Fisher's exact test.
- Resection rate will be compared using Fisher's exact test.
- R0 resection rate will be compared using Fisher's exact test.
- Progression-free survival (PFS) will be compared with a multivariable Cox regression analysis with adjustment for the stratification factors (i.e. resectable versus borderline resectable and institution).
- Locoregional Failure Free Interval and Distant Metastases Free Interval will be compared with a multivariable Cox regression analysis with adjustment for the stratification factors (i.e. resectable versus borderline resectable and institution).
- Toxicity of chemotherapy will be compared using the Fisher exact or chi-square test.
- Postoperative complications will be compared using the Fisher exact or chi-square test.

Sample size calculation

A study from Duke university [31], reported a 3-year recurrence-free survival of 48% in a group of patients with ampullary carcinoma who underwent Whipple procedure alone. A propensity score matched retrospective analyses after R0/R1 resection of Ampullary cancer from our study group the International Study Group on Ampullary Cancer (ISGACA) showed a beneficial effect of adjuvant treatment on overall survival with a hazard ratio of 0.57 [32]. Our primary endpoint is 3-year disease-free survival (DFS) rate, with DFS defined as the time from surgery until disease recurrence or death from any cause. A two-sided test based on the nonparametric estimate of the survival distribution calculated from a sample of 86 patients achieved 90% power (1-beta) at a 0.05 significance level (alpha) to detect a hazard ratio of 0.57, when the proportion of patients free of recurrence at 3 years in the historic control group is 48% (as reported by Palta et al.). Patients are accrued over a 2-year period and followed for 2 more years. The probability that a patient experiences a recurrence at 3 years is 0.34 (corresponding to a 3-year recurrence-free survival =66%). To account for possible loss to follow-up, we intend to enroll 100 patients per stratum (intestinal or PB/mixed subtype).

SAFETY REPORTING

Adverse Events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to [the investigational product / trial procedure/ the experimental intervention]. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded. A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalization or prolongation of existing inpatients' hospitalization;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

All AEs will be followed until they have abated, or until a stable situation has been reached.

REGULATION STATEMENT, RECRUITMENT AND CONSENT

The principal investigator will ensure that this study is conducted in agreement with the Declaration of Helsinki (Tokyo, Venice, Hong Kong and Somerset West, Edinburgh, Washington, Tokyo and Seoul amendments), The protocol has been written, and the study will be conducted according to the ICH Harmonised Tripartite Guideline for Good Clinical Practice and the EU Directives EU clinical trials directive 2001/20/EC and 2005/28/EC.

All patients will be informed of the aims of the study, the possible adverse events, the procedures and possible hazards to which he/she will be exposed. They will be informed of the strict confidentiality of their patient data, but that their medical records may be reviewed for trial purposes by authorized individuals other than their treating physician. It will be emphasized that participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever he/she wants. This will not prejudice the patient's subsequent care. Documented informed consent must be obtained for all patients included in the study before they are randomized at the Data Center. This must be done in accordance with the WMO and ICH guidelines on Good Clinical Practice.

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

Before the study start, the current protocol and the other study documents will be notified to the Ethical Commitee of Brescia

HANDLING AND STORAGE OF DATA AND DOCUMENTS

The principal investigator and the trial management team will guide conduct of the trial according to Good Clinical Practice (GCP). The Local investigators will be responsible for the conduct within their site. Data will be handled confidentially. Each patient will receive an anonymous identification code. To trace data back to an individual patient, a subject identification code list will be used. Each participating site will safeguard the key to this code for patients included at their site. Data will be entered in eCRFs using the electronic online database CASTOR. Data to be collected on the CRF are derived from the protocol. The CRF and instructions for completing the CRF will be provided by the Clinical Trial Center. Automated and manual consistency checks will be performed on newly entered forms; queries will be issued in case of inconsistencies. Consistent forms will be validated by the Clinical Trial Center. Inconsistent forms will be kept "on-hold" until resolution of the inconsistencies.

Monitoring and Quality Assurance

On behalf of the principal investigator, the study will be monitored by an experienced monitor team from the Clinical Trial Center throughout its duration by means of personal visits to the local investigator's facilities and through other communications (e.g. telephone calls, e-mail).

Monitoring visits will take place according to a study specific monitoring plan and will be scheduled at mutually agreeable times periodically throughout the study and at frequency deemed appropriate for the study. These visits will be conducted to evaluate the progress of the study, ensure the rights and well-being of the subjects are protected, check that the reported clinical study data are accurate, complete and verifiable from source documents, and the conduct of study follows the approved protocol and amendments, GCP and applicable national regulatory requirements.

A monitoring visit will include a review of essential clinical study documents (Investigator file, regulatory documents, CRFs, source documents, subject informed consent forms, etc.) as well as discussion on the conduct of the study with the local investigator and staff. Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the CRF are consistent with the original source data.

The principal investigator expects that during monitoring visits the relevant investigational staff will be available, the source documentation will be available and a suitable environment will be provided for review of study-related documents.

Minor and major findings of the monitor will be discussed with the local investigator, and documented in a standard monitoring report that will be provided to the principal investigator. The principal investigator may decide to increase the monitoring frequency or intensity if the results of monitoring require this to ensure patient safety and/or data quality.

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APPENDIX

Dosages, dosage modifications and method of administration

FOLFIRINOX is a combination of systemic chemotherapy agents. mFOLFIRINOX consists of oxaliplatin at a dose of 85 mg/m2, given as a 2-hour intravenous infusion, immediately followed by leucovorin at a dose of 400 mg/m2 given as a 2-hour intravenous infusion, with the addition, after 30 minutes, of irinotecan at a dose of 150 mg/m2, given as a 90-minute intravenous infusion through a Y-connector. This is followed by a continuous intravenous infusion of 2400 mg/m2 over a 48-hour period, every 2 weeks.

About 10% of patients has a (partial) deficiency of the dihydropyrimidine dehydrogenase (DPD) enzyme (encoded by the DPYD gene) resulting in increased fluorouracil toxicity. Testing of the DPYD gene is mandatory.[29]

Fluorouracil dose is adjusted or withheld in patients with a (partial) deficiency of the DPD enzyme following AIOM recommendations. The fluorouracil bolus may be withheld in patients with a WHO/PS 1 and/or age above 75. A modified regimen starting at the first cycle is also allowed at the discretion of the treating physician: irinotecan and oxaliplatin starting dose may be reduced to 80%, and the fluorouracil bolus may be withheld.

Irinotecan is converted in the body to an active metabolite known as SN-38, which is then inactivated and detoxified by a UDP-glucuronosyltransferase (UGT) enzyme encoded by the UGT1A1 gene. The UGT enzymes are responsible for glucuronidation, a process that transforms lipophilic metabolites into water-soluble metabolites that can be excreted from the body.[34] Therefore, it is necessary to test UGT1A1 mutation before the start of the adjuvant therapy. In case of mutations, dose adjustments are required. During treatment the dose reduction should be based on the maximum graded toxicity within the previous cycle, graded using the National Cancer Institute Common Toxicity Criteria (version 4.0.3, see Appendix 2). Dose adjustments follow the AIOM recommendations 2019.[29]

FOLFIRINOX dose adjustment guidelines

Toxicities will be managed by treatment interruption for a maximum of 2 weeks, to allow resolution of toxicity. In the case of illness other than toxicity (i.e. cholangitis), the treatment will be delayed for a maximum of 4 weeks. If a patient's treatment is delayed for longer than 2 weeks because of toxicity or longer than 4 weeks because of illness other than toxicity the patient will discontinue FOLFIRINOX.

After treatment interruption because of toxicity, the dose of one or more agents of the FOLFIRINOX regimen may be reduced according to maximum graded toxicity within the previous cycle as described below. If a dose is reduced because of toxicity, the patient will stay on the reduced dose for the remainder of the study. A second dose reduction is allowed before the patient discontinues from study treatment.

Hematologic toxicity

Do not restart chemotherapy until the granulocyte count is ≥ 1.0 x 10^9 per liter, the platelet count is ≥ 75x109/L and ≥ 1.500 neutrophils per microliter. Granulocyte colony stimulating factor may be used. See tables below.

Table A1. Doses according to the blood counts at the beginning of a cycle (Day 1)

Blood counts Day 1	Delay of cycle	Doses reduction		
		Irinotecan	Oxaliplatin	Fluorouracil
Granulocyte count < 1.5 x 10^9/l	Hold treatment until granulocytes ≥ 1.0 x 109/L (one or two weeks if necessary). In case of non recovery after 2 weeks delay, stop treatment*	1st occurrence: Reduction of dose to 150mg/m^2 2nd occurrence: Maintain the dose at 150mg/m^2 3rd occurrence: Treatment discontinuation	1st occurrence: No reduction of dose 2nd occurrence: Reduce the dose to 60mg/m^2 3rd occurrence: Treatment discontinuation	1st occurrence: Delete bolus 5FU
Platelets <75x109/l=	Hold the treatment until recovery platelets ≥ 75 x 10^9/L. In case of non recovery after 2 weeks delay, stop treatment	1st occurrence: no reduction of dose 2nd occurrence: Reduction of dose to 150mg/m^2 3rd occurrence: Treatment discontinuation	1st occurrence: Reduce the dose to 60mg/m^2 2nd occurrence: Maintain the dose at 60mg/m^2 3rd occurrence: Treatment discontinuation	1st occurrence: Reduce both the bolus and the continuous infusion to 75% of the original doses

Table A2. Doses according to the low nadir blood counts or in case of infection.

Adverse events	**Reduction of dose for subsequent cycles**
Febrile neutropenia OR Grade 4 neutropenia during more than 7 days OR Infection with concomitant grade 3-4 neutropenia	1st occurrence: reduce the dose of irinotecan to 150 mg/m² and delete the bolus 5FU dose 2nd occurrence: reduce also the dose of oxaliplatin to 60 mg/m² 3rd occurrence: treatment discontinuation

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Table A3. Gastrointestinal toxicities.

Adverse events	**Reduction of dose for subsequent cycles**
Diarrhea grade 3-4 or Diarrhea + fever and/or neutropenia grade 3-4	1st occurrence: reduce the irinotecan dose to 150 mg/m2 and delete the bolus 5FU dose 2nd occurrence: reduce also the oxaliplatin dose to 60 mg/m² and reduce the dose of continuous 5FU to 75 % of the original dose 3rd occurrence: treatment discontinuation
Diarrhea ≥ 48 h despite high doses loperamide	No systematic reduction of the irinotecan, oxaliplatin or 5FU doses after complete recovery, unless grade 3-4 diarrhea, or diarrhea + fever, and/or concomitant neutropenia grade 3-4

Patients are instructed to use loperamide for diarrhea, and have a supply of this drug upon starting FOLFIRINOX. Patients should not be retreated with irinotecan until recovery to CTCAE grade ≤1 diarrhea has occurred. See table 10 for details.

Mucositis or "hand-foot" syndrome

In case of grade 3-4 toxicity, delete bolus and reduce continuous 5FU with 25% or the subsequent cycles.

Cardiac toxicity

In case of angina pectoris or of myocardial infarction, 5FU has to be stopped.

Hyperbilirubinemia

In case of elevation of bilirubin, it is suggested to exclude an obstruction of the biliary stent or progressive disease and to postpone chemotherapy. If bilirubin is >1.5xULN, irinotecan is not recommended. If chemotherapy is medically indicated, it is necessary to provide a dose adjustment of irinotecan:

Table A4.

	Irinotecan	Oxaliplatin	5-FU
Bilirubin 1.0 – 1.5 x ULN	75%	100%	100%
Bilirubin 1.5 – 3.0 x ULN	50%	100%	100%
Bilirubin > 3 x ULN	Discontinuation	100%	50%

Other toxicities

Any other toxicity ≥ grade 2, except anemia and alopecia, can justify a reduction of dose if medically indicated, for example reduction of irinotecan to 150mg/m^2 and/or oxaliplatin 60mg/m^2 and or 5-FU 25% depending of the type of adverse event.

CAPOX dose adjustment guidelines

Hematological toxicity

- Delay 1 week if ANC < 1.0 and Platelets < 75
- If delay > 1 week, patient will need a 25% dose reduction of Oxaliplatin and Capecitabine
- No dose reduction for CTC grade I/II ANC

- Grade III/IV ANC → delay chemotherapy until recovered, then proceed at 25% capecitabine and oxaliplatin dose reduction
- If further delay(s) for bone marrow suppression occur despite a 25% dose reduction, consider a further 25% dose reduction

Non-hematological toxicities

Hepatic impairment

- Administration of CAPOX should be interrupted if treatment-related elevations in bilirubin of > 2 x ULN or treatment-related elevations in hepatic aminotransferases (ALT, AST) of > 2.5 x ULN occur.
- Treatment may be resumed when bilirubin decreases to ≤ 2.0 x ULN or hepatic aminotransferases decrease to ≤ 2.5 x ULN.

Table A5. Renal function

GFR	Capecitabine	Oxaliplatin
30-50 ml/min	25% dose reduction	No action
< 30 ml/min	Contact prescriber	Contact prescriber

Neurotoxicity

Cold related paresthesia of hands/feet or dysesthesia/laryngeal spasm syndrome lasting a few hours does not require treatment or dose reduction.

If severe laryngeal spasm occurs, increase oxaliplatin infusion duration to 6 hours

If symptoms persist for 14 days and/or there is pain, functional loss, omit oxaliplatin and continue with capecitabine until recovered, then restart oxaliplatin at 25% dose reduction.

Table A6. Diarrhea

Grade 1 (watery stool 2-3 times/day)	Loperamide 4mg then 2mg QDS PRN
Grade 2 (watery stool 4-6 times/day)	Delay treatment until recovered and give full dose
Grade 3/4 (watery stool >7 times/day)	Delay until recovered and resume treatment at 25% reduced dose of oxaliplatin and capecitabine

Table A7. PPE (hand/foot syndrome) toxicity grading for capecitabine only

Grade	Clinical	Functional	Management
1	Numbness, dysesthesia/paresthesia,	Discomfort but no interruption of normal activities	-
2	Painful erythema with swelling	Discomfort which affects activities of daily living	Interrupt treatment until grade ≤1
3	Moist desquamation, ulceration, Blistering, severe pain	Severe discomfort, unable to work or perform activities of daily living	Interrupt treatment until grade ≤1 and reduce dose by 25%

Table A8. Dose adjustments according to CTC toxicity (Not PPE/hand/foot syndrome)

	Grade 2	Grade 3	Grade 4
1 st appearance	Interrupt treatment until resolved to grade 0/1, then continue at 100% of original dose with prophylaxis where possible	Interrupt treatment until resolved to grade 0/1, then continue at 75% of original dose with prophylaxis where possible	Discontinue treatment
2 nd appearance	Interrupt treatment until resolved to grade 0/1, then continue at 75% of original dose	Interrupt treatment until resolved to grade 0/1, then continue at 50% of original dose	
3 rd appearance	Interrupt treatment until resolved to grade 0/1, then continue at 50% of original dose	Discontinue treatment	
4 th appearance	Discontinue treatment		

Once the capecitabine dose has been reduced, it should not be increased at a later time. Omitted doses are not replaced or restored, instead the patient should resume the planned treatment cycle.