This supplement contains the following items:

1. The final protocol.
2. The summaries of protocol amendments.
3. The statistical analysis plan.

PAC ACCORD

(Concerted actions in colorectal and digestive tract cancers)

PRODIGE 24

PROTOCOL- ACCORD 24

EudraCT N° : 2011-002026-52

Multicentre randomized phase III trial comparing 6-month adjuvant chemotherapy with gemcitabine versus 5-fluorouracil, leucovorin, irinotecan and oxaliplatin (mFolfirinox) in patients with resected pancreatic adenocarcinoma.

Version n°5 (Canada) – 20 June 2012
Approved by the CPP Est III on DD MMM YYYY

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CLINICAL TRIAL AUTHORIZATION
FOR THE PROTOCOL PRODIGE 24 – ACCORD 24

Multicentre randomized phase III trial comparing adjuvant chemotherapy with gemcitabine versus 5-fluorouracil, leucovorin, irinotecan and oxaliplatin (mFolfirinox) in patients with resected pancreatic adenocarcinoma.

CLINICAL TRIAL AUTHORIZATION	
French competent authority (Afssaps/ANSM)	**Date of authorization : 05/08/2011**
	Ref. Afssaps/ANSM : A110755 - 41
INDEPENDENT ETHICS COMITTEE (CPP) **CPP NAME: CPP EST III**	**Date of opinion : 13/10/2011**
	Ref. CPP : 11-07-05

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SYNOPSIS – PRODIGE 24 – ACCORD 24

A) TRIAL IDENTIFICATION

CODE NAME ALLOCATED BY THE SPONSOR : PRODIGE 24 – ACCORD 24

VERSION AND DATE : VERSION N°5 (Canada) – 20 June 2014

TITLE : Multicentre randomized phase III trial comparing adjuvant chemotherapy with gemcitabine versus 5-fluorouracil, leucovorin, irinotecan and oxaliplatin (mFolfirinox) in patients with resected pancreatic adenocarcinoma.

ABRIDGED TITLE : NA

PRINCIPAL INVESTIGATOR : Prof Thierry CONROY, medical oncologist (Unicancer, Nancy)
ASSOCIATE PRINCIPAL INVESTIGATOR : Prof Patrick RAT, surgeon (FFCD, Dijon)

NUMBER OF PARTICIPATING CENTERS (ESTIMATE) : 40	**NUMBER OF PATIENTS :** 490

B) SPONSOR IDENTIFICATION

NAME : UNICANCER

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B) GENERAL INFORMATION

INDICATION : Pancreatic adenocarcinoma (ductal adenocarcinoma)

METHODOLOGY: National multicentre phase III superiority trial comparing standard adjuvant chemotherapy with gemcitabine versus experimental polychemotherapy with mFolfirinox.

PRIMARY OBJECTIVE: to compare disease-free survival (DFS) at 3 years between the experimental and control arms.

SECONDARY OBJECTIVES :

- Overall survival and disease-specific survival
- Metastases-free survival
- Evaluation of toxicity according to the NCI-CTCAE v4.0 scale
- Ancillary translational study (optional).

INCLUSION CRITERIA :

All the criteria listed below are required for inclusion

1. Histologically proven pancreatic ductal adenocarcinoma. Intraductal papillary mucinous tumors of the pancreas (IPMT) with invasive components are eligible.
2. Macroscopically complete resection (R0 or R1 resection).
3. Patients aged from 18 to 79 years.
4. WHO performance status 0-1.
5. No prior radiotherapy and no previous chemotherapy.
6. Full recovery from surgery and patient able to receive chemotherapy: adequate oral nutrition of ≥ 1500 calories per day and free of significant nausea and vomiting
7. Adequate hematologic function (Absolute neutrophil count ANC ≥ 1,500 cells/mm^3, platelets ≥ 100 000 cells/mm^3 and hemoglobin ≥ 10 g/dL - possibly after transfusion -).
8. Serum total bilirubin ≤ 1.5 times the institutional upper limit of normal.
9. Creatinine Clearance ≥ 50 mL/min
10. Patient of child-bearing potential (for female patient: study entry after a menstrual period and a negative pregnancy test) must agree to use two medically acceptable methods of contraception (one for the patient and one for the partner) during the study and for 4 months after the last study treatment intake for women and 6 months for men.
11. Interval since surgery between 21 and 84 days
12. Patient information and signed informed consent.
13. Public or private health insurance coverage

NON INCLUSION CRITERIA

One of the following criteria is sufficient for non inclusion:
1. Other types of non-ductal tumor of the pancreas, including endocrine tumors or acinar cell adenocarcinoma, cyst adenocarcinoma and ampullary carcinoma.
2. Metastases (including ascites or malignant pleural effusion).
3. Macroscopic incomplete tumor removal (R2 resection).
4. CA 19-9> 180 U / ml within 21 days of registration on study.
5. No heart failure or coronary heart disease symptoms
6. No major comorbidity that may preclude the delivery of treatment or active infection (HIV or chronic hepatitis B or C) or uncontrolled diabetes.
7. Pre-existing neuropathy, Gilbert's disease or genotype UGT1A1 * 28 / * 28.
8. Inflammatory disease of the colon or rectum, or occlusion or sub-occlusion of the intestine or severe postoperative uncontrolled diarrhea
9. Concomitant occurrence of another cancer, or history of cancer except in situ carcinoma of the cervix treated or basal cell carcinoma or squamous cell carcinoma.
10. Fructose intolerance.
11. Persons deprived of liberty or under guardianship.
12. Psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule.

PRIMARY ENDPOINT: disease-free survival (DFS) at 3 years.

RANDOMIZATION :
Randomization will be stratified by the following factors :

- center
- nodal status pN0 (< 12 lymph nodes examined versus ≥12 lymph nodes examined) versus pN1
- resection margin : R0 versus R1
- CA19-9 at inclusion ≤ 90 versus CA19-9 between 91 and 180 U/ml

D) INVESTIGATIONAL PRODUCTS

DRUGS :

Drug name (DCI/INN)	Registered name (1)	Pharmaceutical form	Administration	Posology/dosage
Gemcitabine	Gemzar®	Powder for solution for injection	IV	**1000 mg/m²** over 30 minutes infusion, weekly for 3 weeks + 1 week of rest (= 1 cycle) repeated 6 times (6 cycles), i.e. 24 weeks.
Folinic acid	-	Powder for solution for injection	IV	**400 mg/m²** IV infusion over 2 hours
Irinotecan	Campto®	Concentrate for solution for infusion	IV	**150 mg/m²** D1 over 90 minutes to begin 30 min after folinic acid infusion is started
5Fluorouracil	-	Powder for solution for injection	IV	**2.4 g/m²** IV infusion continuous over 48 h (1200 mg/m²/ day)
Oxaliplatin	Eloxatin® or generic drug	Concentrate for solution for infusion Or powder	IV	**85 mg/m²** D1 over 2 hours

(1) In case a generic drug is used, indicate only the DCI name. The choice of the registered or brand name is left to the investigation center.

THERAPEUTIC REGIMENS :

Patients with informed consent signed and matching all inclusion and exclusion criteria will be randomly allocated to received either :

Arm A : Gemcitabine 1000 mg/m² IV infusion over 30 minutes, weekly, during 3 weeks + 1 week of rest (= 1 cycle) repeated 6 times (i.e., 6 cycles) during 24 weeks.
Arm B : mFolfirinox every 14 days, 12 cycles, 24 weeks.

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 : 24 weeks

E) STATISTICAL DESIGN

REQUIRED NUMBER OF PATIENTS :

In total, 490 randomized patients are required to ensure that the 342 events, necessary to demonstrate a 10% increase in DFS at 3 years (from 17% to 27%), are observed. Randomization will be made using the minimization method with a 1:1 ratio and stratified by the following factors: center, lymph node status pN0 (< 12 lymph nodes examined versus ≥12 lymph nodes examined) versus pN1; resection margins (R1 vs R0); postoperative CA 19-9 before inclusion ≤ 90 U / mL vs CA 19-9 in the 91-180 range.

An early tolerance analysis will be conducted, after the first 30 patients included have received 2 cycles of treatment, to ascertain that the rate of grade 3-4 diarrhea does not exceed 5%. Otherwise, the dose of irinotecan will be reduced to 150 mg/m^2.
An interim analysis of the main criterion is scheduled after 113 first events are observed.
An early stopping rule will be applied in case the toxic death rate exceeds 2%.

STATISTICAL ANALYSIS :

The detailed statistical analysis plan (SAP) will be elaborated before the I/O on the database is frozen for the interim analysis.
Qualitative variables will be presented using their frequency values and percentages, and comparison between the treatment groups will be made with the chi-2 test. Quantitative variables will be presented using their average value, standard deviation, median value and range. Comparison between treatment groups will be made with the Student T-test or Kruskal-Wallis test according to the case. Toxicity grades will be compared with the non-parametric test of Kruskal-Wallis. Disease-free survival will be defined as the time elapsed between patient randomization and first event occurrence such as local relapse, metastatic relapse, second cancer or death from any cause. The effect of the experimental treatment relative to the control arm effect will be presented with its hazard ratio and CI95% confidence interval. Prognostic factors for disease recurrence will be evaluated with the Cox model and all analyses performed on an Intention-to-treat (ITT) basis.

F) BIOLOGICAL SAMPLES COLLECTED FOR THE TRANSLATIONAL STUDY

SAMPLE(S) TYPE(S): Tumor and blood

QUANTITY COLLECTED : 10 ML

G) TRIAL DURATIONS

INCLUSION PERIOD: 3 years

TREATMENT DURATION: 24 weeks

FOLLOW-UP PERIOD : 5 years

EXPECTED TRIAL DURATION BEFORE THE MAIN OBJECTIVE IS ANALYZED : 6 years

OVERALL TRIAL DURATION (INCLUDING FOLLOW-UP) : 8 years

H) TREATMENT MONITORING AND EXAMINATION SCHEDULE

Arm A = 6 months treatment

Monitoring ARM A, gemcitabine															
Visit	**Baseline visit**	**Follow up visits**					**Visit at 3 months**	**Follow up**							**Follow up after treatment[4]**
Visit N° (V)	**V0**	**V1, 2,3**	**V4**	**V5,6, 7**	**V8**	**V9,10 ,11**	**V12**	**V13, 14,15**	**V16**	**V17 18, 19**	**V20**	**V21, 22, 23**	**V24**	**VF (2-4 weeks)**	
Date	**D0**	**D1, D8, D15**	**D22**	**D29, D36, D43**	**D50**	**D57, D64, D71**	**D78**	**D85, D92, D99**	**D106**	**D113, D120, D127**	**D134**	**D141, D148, D155**	**D162**		
Signed informed consent form	**X**														
Inclusion / non inclusion criteria	**X**														
Randomization	**X**														
Clinical Examination															
Weight	**X**			**X**		**X**	**X**	**X**		**X**		**X**		**X**	**X**
Height	**X**						**X**							**X**	**X**
WHO performance	**X**	**X**		**X**		**X**	**X**	**X**		**X**		**X**		**X**	**X**
Neurological Examination	**X**													**X**	**X**
Concomitant treatments	**X**														
Toxicities (2)															
Evaluation of the tolerance		**X J8 et J15**		**X**		**X**	**X**	**X**		**X**		**X**		**X**	**X**
Examen Biologique (3)															
WBC, platelets	**X**	**X**		**X**		**X**		**X**		**X**		**X**			
Calcium	**X**														
Electrolytes	**X**	**X**		**X**		**X**		**X**		**X**		**X**			
Protein	**X**	**X**		**X**		**X**		**X**		**X**		**X**			
Albumine	**X**														
Hepatic Functions	**X***	**X****		**X****		**X****		**X****		**X****		**X****			
Serum Créatinine	**X**														
Creatinine Clearance	**X**														
Serum glucose	**X**	**X**		**X**		**X**		**X**		**X**		**X**			
CA 19-9	**X**						**X**							**X**	**X**
Pregnancy test	**X(1)**														
Paraclinical tests (5)															
TAP CT Scan (6)	**X**						**X**							**X**	**X**
ECG	**X**														
Translationnal Research															
Recuperation of the biopsy at diagnosis	**X**														
Blood sampling 10 ml EDTA (2 x 5 ml)	**X**														

* *Hepatic function evaluation alkaline phosphatase, total, free and conjugated bilirubin, ALT and AST*

** *Hepatic function evaluation with total, free and conjugated bilirubin, ALT and AST*

(1) For women of child bearing age without efficient contraception

(2) Serious adverse event (SAE) to be declared within 48 hours to the sponsor until the 30th days after the end of the last chemotherapy course. Beyond that period, only SAEs that may be imputed to the research will be declared to the sponsor, provided that no other cause can be reasonably identified.

(3) Baseline biological tests must be performed within a 7-day delay preceding randomization and within 84 days after surgery.

(4) Every 3 months during the first 2 years and every 6 months thereafter, during 3 years.

(5) Paraclinical exams must be perform 30 days before the randomization date and maximum 84 days before surgery

(6) or MRI Abdomino pelvien **and** thoracic scan in case of allergy to contrast agent.

Patients with disease progression will be monitored every 6 months until they die. Long-term toxic effects and survival will be evaluated. In case another treatment is set up, it will be reported.

Arm B
12 cycles scheduled = 6 months treatment

Monitoring schedule : BRAS B mFolfirinox															
Visit	**Baseline**	**Follow up every 14 days**							**Visit at 3 months**	**Follow up every 14 days**					**Followup after treatment[4]**
Visit N°	**V0**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**VF entre 2 et 4 sem**	
Day	**D0**	**D1**	**D15**	**D29**	**D43**	**D57**	**D71**	**D85**	**D99**	**D113**	**D127**	**D141**	**D155**		
Siogned Informed Consent form	**X**														
Inclusion / non inclusion criteria	**X**														
Randomization	**X**														
Clinical Examination															
Weight	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Height	**X**								**X**					**X**	**X**
WHO performance	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Neurological Examination														**X**	**X**
Concomitant treatments	**X**														
Toxicities (2)															
Evaluation of the tolerance			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Biological Examination (3)															
WBC, platelets	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**		
Calcium															
Electrolytes	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**		
Protein	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**		
Albumine	**X**														
Hepatic Functions	**X***	**X****	**X****	**X****	**X****	**X****	**X****	**X****	**X****	**X****	**X****	**X****	**X****		
Serum Créatinine	**X**	~~**X**~~													
Creatinine Clearance	**X**														
Serum glucose	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**		
CA 19-9	**X**								**X**					**X**	**X**
Pregnancy test	**X**(1)														
Paraclinical tests (5)															
TAP CT Scan (6)	**X**								**X**					**X**	**X**
ECG	**X**														
Translational research															
Recuperation of the biopsy at diagnosis	**X**														
Blood sampling 10 ml EDTA (2 x 5 ml)	**X**														

* *Hepatic function evaluation: alkaline phosphatases, total, free and conjugated bilirubin, ALAT and AST*
** *Hepatic function evaluation with total, free and conjugated bilirubin, ALAT and AST*
(1) For women of child-bearing age without efficient contraception.
(2) Serious adverse event (SAE) to be declared within 48 hours to the sponsor until the 30th day after the end of the last chemotherapy course. Beyond that period, only SAEs that may be imputed to the research will be declared to the sponsor, provided that no other cause can be reasonably identified.
(3) Baseline biological tests must be performed within a 7-day delay preceding randomization and within 84 days after surgery.
(4) Every 3 months during the first 2 years and every 6 months thereafter, during 3 years.
(5) Paraclinical exams must be perform 30 days before the randomization date and maximum 84 days before surgery
(6) or MRI Abdomino pelvien and thoracic scan in case of allergy to the contrast medium

Patients with disease progression will be monitored every 6 months until they die. Long-term toxic effects and survival will be evaluated. In case another treatment is set up, it will be reported.

TABLE OF CONTENT

UNICANCER the study sponsor declares that the *PRODIGE 24 – ACCORD 24/0610* trial will be conducted in accordance with this protocol, the Code de la Santé Publique articles 1121-1 and the related decrees and orders in force as well as the Good Clinical Practices (GCP) as defined on November 24, 2006.

1. INTRODUCTION AND RATIONALE OF THE STUDY

1.1 Study Rationale

1.1.1 Epidemiology of pancreatic cancer

Due to its high occurrence and severity, cancer of the exocrine pancreas has become a serious public health problem, especially in developed countries. It was the cause of 227,000 deaths in 2002 worldwide, i.e., the 8th most lethal cancer (Ferlay J et al. 2002). In the United States, it is the 4th cause of cancer death in both genders. According to the estimations for 2010, 43,140 new cases and 36,800 deaths were foreseen in the USA (Jemal A et al. 2010) with 6% survival at 5 years in men and 7 % in women. In Europe, the estimated number of deaths was 70,200 (Ferlay J et al. 2010) in 2002 which represents the 5th cause of cancer death. According to the Eurocare cancer registry, the 5-year survival was only 5.5 % (Eurocare-4, Berrino F et al. 2007).

In France, according to the data from the Institut National de Veille Sanitaire (National Institute for Health Monitoring), the incidence was 7,218 new cases and 7,787 deaths in 2005 which represents the 5th cause of cancer deaths. The median age at diagnosis was 69 years for men (55%) and 74 years for women. The incidence of pancreatic cancer is increasing rapidly. Between 1978 and 2000, the annual incidence increased from +1.27 % in men and +2.07 % in women. The incidence expected in 2010 was 10,133 new cases. More than 90 % of pancreas cancer cases are exocrine tumors with more than 90% of ductal adenocarcinomas, including rare variant forms such as mucinous noncystic cancers, adenosquamous cancers, undifferentiated or anaplastic or giant cells osteoclastic cancers. Patients with mucinous adenocarcinomas (about 1 % of cases) have a relatively good prognosis compared with those presenting ductal adenocarcinomas. This type of tumor is usually not included in adjuvant chemotherapy studies.

Most patients present a locally advanced or metastatic disease. A study carried out on 1175 cases from the Calvados cancer registry (Lefebvre AC et al. 2009) shows that, between 1978 and 2002, only 11.5% of patients have undergone a potentially curative surgery. The surgical resection percentage has increased significantly during the last period studied (1998-2002), but remains weak (13.4 % of cases). The median survival of patients having undergone curative surgery with negative resection margins (R0 resection) is around 2 years with 5-year survival about 15 to 20 % (Philip PA et al. 2009). The fact that a large number of patients, who were initially diagnosed with a loco-regional disease and who underwent potentially curative surgery, died rapidly suggests that a high percentage of them had undetected distant metastasis.

1.1.2 Prognostic factors after surgical resection

1.1.2.1 Usual/standard prognostic factors

The most important prognostic factor in pancreatic cancer treatment is the possibility of curative resection which is the only intervention that allows prolonged survival. Medical team specialization has allowed the peri-operatory mortality to be reduced, with a clear correlation between hospital volume (number of operated patients) and mortality (Birkmeyer JD et al. 2002). Studies on prognostic factors that included more than 100 patients operated with curative intent are limited in numbers (Table 1), while the knowledge of prognostic factors is essential to select stratification criteria and to avoid unbalances between treatment arms in phase III trials.

Table 1: Independent prognostic factors after curative resection of a ductal pancreatic cancer

Series	Lim 2003	Kuhlmann 2004	Slidell 2008	Chang 2009	You 2009	Hsu 2010	Berger 2008
N patients	396	160	4505	395	219	1092	385
Prognostic factors	T < 2 cm N Grade Center Adj. RCT adj. Income	N Margins T (cm wise)	T N Ratio N+/N Grade Nb of nodes examined	Loci. Head T < 2 cm Margins > 1.5 mm N. Vascul. Embols Adjuvant Chem.	N Grade T > 3 cm	Age > 70 yrs T3 Grade N Margins RCT adj.	N Margins CA 19-9 ≥ 90 or 180

In the series of 396 patients from the **SEER database** (Lim JE et al. 2003), the favorable prognostic factors are: tumor size < 2 cm, no lymph node involvement, good histological differentiation, surgery performed in a research hospital, adjuvant radiochemotherapy and high socio-economic status (SES).

In a multifactorial analysis based on the SEER database and carried out on 4 505 patients operated between 1988 and 2003 (Slidell MB et al. 2008), the prognostic factors related to the tumor were: tumor differentiation, tumor size, the number of positive lymph nodes, the nodal status (N0 vs N1) and the ratio of the number of invaded lymph nodes / number of lymph nodes examined. For N0 tumors, the median survival is16 months when less than 12 lymph nodes have been examined versus 23 months when the pathologist has examined at least 12 nodes ($p < 0.001$). The interest of the study is to demonstrate that for N0 tumors, a threshold of 12 lymph nodes examined is the discriminating factor and that a minimum of 12 lymph nodes must be examined to have reliable staging.

The Mayo Clinic has reviewed 472 files of patients operated with curative intent (Corsini MM et al. 2008). The risk factors for relapse were lymph node involvement, a high histological grade and the absence of adjuvant radiochemotherapy.

Clinical-pathological data from a cohort of 365 consecutive patients with ductal adenocarcinomas and having undergone R0 resection were collected in 8 **hospitals of Sidney** between 1990 and 2007. Mutlivariate analysis of these data has showed that tumor site (better patient survival for tumors of the head of pancreas), tumor size ≤ 20 mm, positive resection margins, lymph node metastases, vascular invasion and adjuvant chemotherapy are independent prognostic factors (Chang DK et al. 2009).

The Johns Hopkins Hospital has reviewed the files of 616 patients operated between 1993 and 2005 (Herman JM et al. 2008). With invaded margins (44.6 % of cases) survival was 13.9 %, whereas it was 20.3% with clear resection margins ($p=0.001$). A pooled analysis of these two series (n=1092) was published in 2010 (Hsu CC et al. 2010). In 68 % of cases, tumor specimens had invaded lymph nodes and in 33.2% positive margins. Patient's age ≥ 70 years corresponded to a 20 % mortality increase compared with patients < 70 years (median survival = 17.5 months vs. 19.7 months; $p=0.008$). Other unfavorable prognostic factors were T3 stage, poor histological differentiation, and lymph node invasion and resection margin positivity. All these factors increased the risk of death by about 45 % (relative risks from 1.44 to 1.47, $p < 0.001$ in all cases). Compared with patients having undergone surgery with follow-up, adjuvant radiochemotherapy significantly improved the median survival (21.1 months vs 15.5 months) with a survival benefit at 5 years: 22.3 % vs. 16.1 % ($p < 0.001$). Four hundred and nighty six (496) patients were subjected to matched sampling according to prognostic factors to remove possible observational bias. This analysis confirmed the improvement with adjuvant radiochemotherapy (median = 21.9 months vs. 14.3 months). The difference in 5-year survival was even larger (25.4 % vs. 12.2 %), which reflects the fact that adjuvant radiochemotherapy was offered to patients younger but presenting more serious tumor characteristic in terms of differentiation and margin positivity. Using the propensity score method to adjust odds ratios for confounding factors, the benefit of radiochemotherapy appeared to be independent from the margins and lymph node status.

Neither the historic **EORTC** study (Klinkenbijl JH et al. 1999) nor the ESPAC-1 study (Neoptolemos JP et al. 2001) could evidence the benefit of adjuvant radiochemotherapy again. The randomized phase II study of FFCD and EORTC (Van Laethem JL et al. 2010) also failed in this respect. It is to be noted that in both the Johns Hopkins Hospital and Mayo Clinic studies, performance status, comorbidities and post-operatory

recoveries were not known for all patients, which may have induced a bias. In addition, data on local relapse were not available.

In a series of 219 Korean patients (You D et al. 2009) having undergone cephalic duodenoprancreatectomy (DPC), prognostic factors were lymph node invasion, tumor differentiation and tumour size > 3 cm.

In a series of 160 patients from the Hospital of Amsterdam and who had undergone surgery with curative intent (Kuhlmann KF et al. 2004) three independent prognostic factors were identified as unfavorable in a multifactorial analysis: lymph node invasion, positive resection margins and tumor.

In a meta-analysis based on **ESPAC** (Butturini G et al. 2008), unifactorial prognostic factors were tumor grade, lymph node involvement and tumor size. This meta-analysis showed that the invasion of resection limits was not a significant prognostic factor, however only 31% of tumor specimens were R1. The percentage of positive margins is tightly related to specimens staining and the techniques used, and it increases considerably when the collaboration between the surgeon and pathologist is optimal and a standardized protocol is used.

1.1.2.2 Assessing resection margins accurately

Three resection margins are important to assess whether the invasion is R0 or R1. The pathological report must also include the status of the 3 margins making contact with the bile duct, the pancreatic parenchyma, and the medial margin. The importance of the posterior and medial margins (see appendix 3) in pancreatic cancer is acknowledged in the AJCC manual (Greene FL *et al*. 2006), and in the recommendations of the College of American Pathologists.
(http://www.cap.org/apps/docs/committees/cancer/cancer_protocols/2009/PancreasExo_09protocol.pdf http) wherein they are defined as 'deep radial posterior margin' and 'uncinate margin'. These two recommendations advocate the staining of these margins. Similarly, the Royal College of Pathologists (http://www.rcpath.org/resources/pdf/datasethistopathologicalreportingcarcinomasmay10.pdf) recommends staining of the anterior, medial and retro-peritoneal margins of the resected tissues. Medial and posterior margins of operative specimens in pancreas cancer are most often infiltrated (Esposito I *et al.* 2008). In this team using standardized anatomicopathological examination the percentage of resection limit positivity increased from 14% (control group: 2002-2004) to 76% in 111 operative specimens studied between 2005 and 2006.

A first study, using a standardized anatomo-pathological technique, conducted by a research team from Leeds (Verbeke CS et al. 2006) reported a R1 rate of 85%. In a second study, 22/27 (82%) operative specimens were classified R1, with the medial (SMV groove) and posterior pancreatic margin considered the most important (invaded 12 and 13 times, respectively); the margin status is correlated with survival in pancreatic cancer (P = 0.046).

In the series from Sidney (Chang DK et al. 2009), multivariate analysis have been performed with different definitions for R1. Results suggest that margins > 1.5 mm are associated with longer survival. Similarly, the resection limit status defined with R1 ≤ 1.5 mm appeared to be an independent predictive factor for survival in multivariate analysis.

In a Belgium retrospective analysis conducted on a series of 145 consecutive pancreatic cancer resections, with a margin ≤ 1 mm considered as invaded the resection margin status became a strong prognostic factor (Van den Broeck A *et al*. 2009).

1.1.2.3 Post-operatory prognostic value of CA 19-9

A small series (Montgomery RC et al. 1997) suggested the prognostic impact of the post-operative dosage of serum CA 19-9. This was confirmed by several series of operated patients (Boeck S et al. 2006; Ferrone CR et al. 2006; Smith RA et al. 2008) . In the series from the Memorial Hospital, including 111 patients (Ferrone CR et al. 2006), prognostic factors in multifactorial analysis were the post-operative drop of CA 19-9, N stage N, T stage and post-operatory CA 19-9 < 200 U/mL.

The RTOG **97-04** study has allowed this result to be confirmed in 385 operated patients for whom the dosage of serum CA 19-9 was performed within 3 weeks preceding inclusion in the adjuvant treatment or after randomization, but before adjuvant treatment. Only patients belonging to the Lewis positive blood group

(who can express CA 19-9) were eligible (only 66 % in this series). Survival was significantly reduced when post-operative CA 19.9 was ε 180 U/mL (8.6% of cases) with a relative risk of death HR = 3.58 (p < 0.0001). Results are similar with a cut-off of 90 U/mL and the authors suggest to stratify or to exclude from future adjuvant trials the patients with CA 19.9 ≥ 90 U/mL. Other prognostic factors were lymph node invasion, and resection limit status, whereas tumor size was not a significant prognostic factor (Berger AC et al. 2008). Another study showed that the decrease rate of CA 19.9 is a better indicator of survival than the CA 19.9 dosage at diagnosis (Hernandez et al. 2008). The ongoing RTOG (0848) trial anticipates the exclusion of patients with CA 19-9 > 180 U/mL after surgery. The patients are stratified by the lymph node status, margins status and CA 19-9 value (≤ 90 vs 91-180).

1.1.3 Adjuvant chemotherapy: literature background

Adjuvant chemotherapy after a duct adenocarcinoma of the pancreas has become a standard since the results of the ESPAC-1 and CONKO-001 trials have been published. The first study of the European Study Group for Pancreatic Cancer (ESPAC) was conducted between 1994 and 2000 in 11 countries (Neoptolemos JP et al. 2001). Eligible patients (n=451) were randomized according to a factorial design to test the value of adjuvant radiochemotherapy (finally deemed deleterious) and adjuvant chemotherapy based on 5-FU. Chemotherapy consisted of 6 cycles of Mayo Clinic type FUFOL (5-FU bolus 425 mg/m²/day and folinic acid 20 mg/m²/day from D1 to D5; next cycle starting on D29). The analysis gathered three types of randomization, making its interpretation difficult. A further analysis, comparing 142 patients without chemotherapy versus 147 patients who had received 5-FU and folinic acid concluded that there was a significant survival benefit in favor of adjuvant chemotherapy, with the median survival increasing from 15.5 months (surgery alone) to 20.1 months (with adjuvant chemotherapy). With chemotherapy, 2-year survival raised from 30 to 40 % and 5-year survival from 8 to 21 % (Neoptolemos JP et al. 2004). In a further meta-analysis (Stocken DD et al. 2005), chemotherapy was found to be beneficial for all prognostic categories: age, tumor differentiation, lymph node status and tumor size (≤ 2 cm vs. > 2 cm).

A second phase III study, CONKO-001 (Charité ONKOlogie), has compared gemcitabine adjuvant chemotherapy with a monitoring only in 368 patients who underwent intervention with curative intent (Oettle H et al. 2007). Gemcitabine administered dose was 1000 mg/m² on D1, D8, D15 every 4 weeks for 6 months. Patient characteristics were well balanced between the 2 arms. Relapse-free survival, the main objective of the study, was significantly prolonged in the gemcitabine arm (13.4 months versus 6.3 months; p < 0.001). The benefit of gemcitabine was observed irrespective of the margin status, resection quality (R0 or R1) and lymph node status. By the time results were published, there was no difference in median survival (22.1 versus 20.2 months; p = 0.006), but a tendency towards improvement of survival in the gemcitabine arm (34% vs. 20.5% at 3 years). However, a study update was presented at the ASCO symposium in 2008 (Neuhaus P et al. 2008) showing the study had turned a positive result with a 5-year overall survival of 21 % in the gemcitabine arm versus 9 % in the surgery alone arm (p = 0.005).

Later on, the beneficial effect of gemcitabine was confirmed by a study carried out on a small cohort (n= 119) in Japan (Ueno H et al. 2009). Significant relapse-free survival benefit was shown in the whole patient population with the median relapse-free survival increasing from 5 months with monitoring alone to 11.4 months with adjuvant chemotherapy using gemcitabine (p = 0.01). We find again the favorable effect of gemcitabine irrespective of the resection status R0 or R1.

RTOG (study **97-04**) has compared 5-FU I.V. continuous infusion (250 mg/m²/day) with adjuvant gemcitabine (Regine et al, 2008). In total, 538 patients were included, of whom 451 were eligible. All patients received 3 weeks of one of the two chemotherapies followed by radiochemotherapy (5-FU continuous infusion in both arms), followed by 3 months of adjuvant chemotherapy. The main objective was to prolong overall survival, and survival in the patient subgroup with cancer of the head of pancreas. This study had two disadvantages: a high rate of ineligible patients (16 %) and unbalanced tumor characteristics at inclusion, disadvantaging the gemcitabine group in particular. In the subgroup of patients affected by an adenocarcinoma of the head of pancreas (n=388), the median survival in the gemcitabine arm was 20.5 months versus 16.9 months in the 5-FU arm (p = 0.09; HR 0.82 [95% IC, 0.65-1.03]). After adjustment for other variables, the effect was hardly significant (p = 0.05). Hematological toxicity was significantly higher in the gemcitabine arm.

RTOG 97-04 has also confirmed the impact of post-operative CA 19-9 on prognosis in 385 operated patients with dosage of CA 19-9 within 3 weeks preceding inclusion in the trial or after randomization, but before adjuvant treatment. Survival was significantly reduced with post-operative CA 19.9 > 180 U/mL (8.6% of

cases) with a relative risk of death HR = 3.58 (p < 0.0001). The authors suggest that patients with CA 19.9 ≥ 90 U/mL be stratified by this criterion or excluded from the future trials.

The two types of adjuvant chemotherapy, 5-FU plus folinic acid versus gemcitabine, have been compared in the ESPAC-3 study (Neoptolemos J et al. 2010) including 1088 patients. The objective was to detect a 10% increase in the 2-year survival with gemcitabine. Most of the patients were included in English, German, Australian and Canadian centers. In terms of relapse-free survival (14.1 months versus 14.3 months) and median survival (23 months versus 23.6 months), the two arms (5FU/folinic acid and gemcitabine) were strictly similar. On the contrary, tolerance of gemcitabine was better regarding grade 3-4 mucositis (0 % versus 10 %; p < 0.001) and grade 3-4 diarrhea (2 % versus 13 %; p < 0.001).

Gemcitabine monotherapy remains thus the reference treatment in adjuvant chemotherapy. The protocol will compare it with Folfirinox.

1.1.4 Rationale supporting Folfirinox chemotherapy in the adjuvant setting

The **PRODIGE 4-ACCORD 11/0402** study was conducted within the framework of PRODIGE (FFCD + UNICANCER, now Unicancer). This study has compared first line chemotherapy with FOLFIRINOX (5-FU, folinic acid, irinotecan and oxaliplatin), in patients with measurable metastatic disease, with gemcitabine monochemotherapy which is the reference treatment in the metastatic setting. Only patients with good performance status WHO = 0 or 1 and normal or subnormal bilirubin (value < 1.5 the upper limit of normal), and without major cardiac impairment, who could benefit from polychemotherapy, were included. The randomized phase II study began in January 2005 with the objective response rate as the primary objective. Results were presented at the ASCO symposium in 2007: after external review, the response rate was 31.8 % in the FOLFIRINOX arm versus 11% for gemcitabine (Ychou M et al. 2007).

Following this encouraging result, the phase III PRODIGE 4 study was opened in 48 centers in May 2007. The phase III objective was to improve the median survival by 3 months (from 7 months in the gemcitabine arm to 10 months in the FOLFIRINOX arm; HR = 0.70 with 80% power and 〈 = 0.05). However, the study was prematurely terminated at the end of September 2009 following an IDMC unfavorable report based on the programmed interim analysis showing the occurrence of 192 adverse events in 3420 over the 360 scheduled inclusions. The study final analysis was orally communicated at the ASCO symposium in 2010.

These results brought a piece of evidence of the benefit of Folfirinox with respect to gemcitabine. The 1-year survival was clearly prolonged (2.4 longer) without negative impact on the quality of life. However, Folfirinox was significantly more toxic than gemcitabine with 45.7% of patients with grade 3/4 neutropenia, and 5.4% with febrile neutropenia. Grade 3-4 thrombocytopenia was also more frequent in the Folfirinox arm (9.1 % versus 2.4 %). Folfirinox is a type of chemotherapy that is also more tiring according to the investigators (23.2 % versus 14.2 % grade 3-4 fatigue; ns), however, no difference in the fatigue score was recorded in the quality of life forms filled out by the patients. Folfirinox induces significantly more diarrhea (12.7 % versus 1.2 %). One toxic death occurred in each arm. Near 45 % of patients received 12 cycles of Folfirinox or more, over a period of 6 months in which the disease made no progress.

The phase III final response rate was 31.6 % in the Folfirinox arm versus 9.4 % in the gemcitabine arm (p < 0.0001). The disease control rate was 70.2 % with Folfirinox versus 50.9 % with gemcitabine (p < 0.0003). Progression-free survival was significantly prolonged in patients receiving Folfirinox: 6.4 months versus 3.3 months with gemcitabine (p < 0.0001). After a median follow-up of 26.6 months, the median survival was 11.1 months with Folfirinox versus 6.8 months with gemcitabine (p < 0.0001); i.e., the median de survival was extended by 4.3 months, which was an unprecedented result. Survival at 1 year was 48.4 % for patients treated with Folfirinox versus 20.6 % for those receiving gemcitabine (hazard ratio HR = 0.57, 95% confidence interval CI95%: 0.45-0.73). Overall survival after progression and second line therapy was similar in both arms.

Quality of life was not statistically different between the two treatment arms with, however, more pain in the gemcitabine arm and more diarrheas in the Folfirinox arm, especially during the first 4 months of treatment. Improvement of the overall quality of life, fatigue and pain were observed in both arms. Irreversible deterioration of the overall quality of life, with a drop of 10 points or more, was faster with gemcitabine (HR = 1.45; CI 95 %: 1.15-1.83). Similar results were obtained for all tested quality-of-life related items, except for diarrhea and financial problems (no difference observed).

The benefit of Folfirinox was demonstrated for all prognostic categories: age, sex, performance status, albumin level, primary tumor site, synchronous or metachronous metastasis, number of metastatic sites, presence or absence of hepatic metastasis, CA 19-9 and ACE dosages. In multifactorial analysis, favorable prognostic factors were in the allocated arm for Folfirinox, age ≤ 65 years, normal albumin level, metachronous metastases, and the absence of hepatic metastasis (Conroy et al. 2011).

In total, the **PRODIGE 4-ACCORD 11/0402** study has defined a new therapeutic standard for patients with metastatic disease and good performance status (Kim R, 2011). These results support the setup of an adjuvant chemotherapy study comparing standard chemotherapy with gemcitabine against the new Folfirinox protocol, since potential problems of elevated bilirubin levels (which delay the irinotecan elimination) will not be very probable in the adjuvant setting. To take into account the hematological toxicity of Folfirinox, 5–FU bolus will be cancelled since it is the main cause of hematological toxicity. Considering a median survival benefit of 4.3 additional months in the metastatic setting, it is reasonable to expect a superior benefit in the adjuvant setting (i.e., to increase the disease-free median survival from 14 months with gemcitabine to 19 months with Folfirinox, and the 3-year disease-free survival from 17% to 27%).

Possible indications for adjuvant radiochemotherapy after adjuvant chemotherapy in case of R1 resection are not a consensus and were discussed with the board of the French Society of Oncologic Radiotherapy (SFRO). The most recent randomized adjuvant trial is the phase II EORTC and FFCD 03-04 study on pancreatic cancer that has compared 4 cycles of gemcitabine vs. 2 cycles of gemcitabine followed by continuous radiotherapy 50.4 Gy (28 fractions of 1.8 Gy) and gemcitabine 300 mg/m^2 weekly during the 5 weeks of radiotherapy (van Laethem et al., 2010]. The rate of local relapse as first relapse site seemed reduced in the experimental arm (11% vs. 24%; significance not tested). Relapse-free median survival (main objective) was 11.8 months in the experimental vs. 10.9 months in the control arm (p=0.6) with an overall median survival of 24 months in both arms. These not very encouraging results do not allow the recommendation of radiotherapy, the possible utility of which is assessed in the EORTC-RTOG 0848 trial.

After discussing the matter in the pancreas group of study and the scientific committee of PRODIGE, it was decided to test 6-month adjuvant chemotherapy with FOLFIRINOX versus gemcitabine under the precaution of early termination criteria in case of severe toxicity.

1.1.5 Pathology of the exocrine pancreas tumors

a. Solid tumors

Exocrine adenocarcinomas represent 95 % of pancreatic tumors. Endocrine tumors require a different type of treatment and are not eligible for this protocol. This also holds for the pancreatic intra-epithelial neoplasia that is not an invasive tumor, and the intraductal papillary mucinous tumors of the pancreas (IPMT). On the contrary, mucinous or ductal degenerated IPMTs (with invasive component) are eligible for this protocol.
Among duct-adenocarcinomas, histological variants (mucinous adenocarcinoma, independent cell adenocarcinoma, adenosquamous carcinoma, anaplastic carcinoma (undifferentiated), mixed ductal-endocrine carcinoma, osteoclast-like giant cell tumor) are eligible.

Major prognostic factors will be evaluated, not only to better describe the study populations but also to better interpret the data from translational research:

- Histological grade: well, moderately and poorly differentiated tumor,
- tumor size (in the largest dimension),
- number of lymph nodes examined,
- number of invaded lymph nodes,
- resection margin invasion: pancreatic slice (cross-section), posterior slide, surgical limits with respect to the mesenteric blood vessels (medial margin, cf. appendix 3),
- R0 versus R1
- nerve sheathing,
- endo-venous and endo-lymphatic vascular emboli,
- tumor site: head of pancreas (uncinate process included), body and tail (several site are possible),
- neighbor-organ invasion,
- no mention of visceral metastasis in the operative report,
- pTNM 2009 classification.

Acinar cell carcinomas are rare; they are excluded from the protocol due to their seriousness, the unknown efficacy of chemotherapy and difficulty to stratify exceptional tumors.
Similarly, pancreatoblastomas, more frequent in children than adults, are excluded from the protocol.

b. Cystic tumors

Cystic lesions (cystadenocarcinomas) represent only 1 % of pancreatic cancers, but as much as 5 % of those that are operated. Their prognosis is better than that of duct adenocarcinoma. Because the efficacy of adjuvant chemotherapy is not known for this type of tumor and because it is not possible to stratify the population of patients by multiple factors, it was decided to also exclude them the protocol. This is the consensus approach in all currently ongoing protocols.

1.2 Study population

The study population comprised men and women aged between 18 and 79 years who are affected by a cancer of the exocrine pancreas.

2. STUDY OBJECTIVES

2.1 Main objective

To compare disease-free survival at 3 years between the experimental and control arms.

2.2 Secondary objectives

To compare between the two arms:

- Overall survival and specific survival
- Metastasis-free survival
- Evaluation of the toxicity according to the NCI-CTCAE v4.0 classification (appendix 12).
- Ancillary translational study (optional).

3. STUDY DESIGN

3.1 Evaluation criteria

3.1.1 Main criterion: efficacy

The main criterion is the disease-free survival at 3 years.

Disease-free survival is the time delay between the date of randomization and the date at which the 1st cancer-related event such as local relapse, distant metastasis, a second cancer or death from any cause is observed. Patients without event at the time of analysis will be censored at the date of last follow-up visit.

Loco-regional relapse is a disease relapse occurring at the site of primary resection, in the pancreas or in the associated regional lymph nodes.

Metastatic relapse is the distant disease recurrence involving any possible sites of relapse (peritoneal, hepatic, pulmonary, and distant lymph nodes).

3.1.2 Secondary criteria

3.1.2.1 Overall and specific survival

Overall survival is the time delay between the date of randomization and the patient's death, irrespective of its cause. Patients who are still living at the time of analysis will be censored at the date of last follow-up visit.

Specific survival is the time delay between the date of randomization and the patient's death due to the treated cancer or a treatment-related complication.

3.1.2.2 Metastasis-free survival

Metastasis-free survival is the time delay between the date of randomization and the date of the 1st distant event occurrence (peritoneal, hepatic, pulmonary, and lymph nodes). Loco-regional events will be discarded and patients still living without metastasis at the time of analysis will be censored at the date of last follow-up examination objectively assessing this type of event.

3.1.2.3 Tolerance

Patients evaluable for toxicity must have received at least one course or injection of the treatment.

- Toxicity will be evaluated according the toxicity scale NCI-CTCAE version 4.0 (appendix 12).

3.1.3 Biological study (appendix 14)

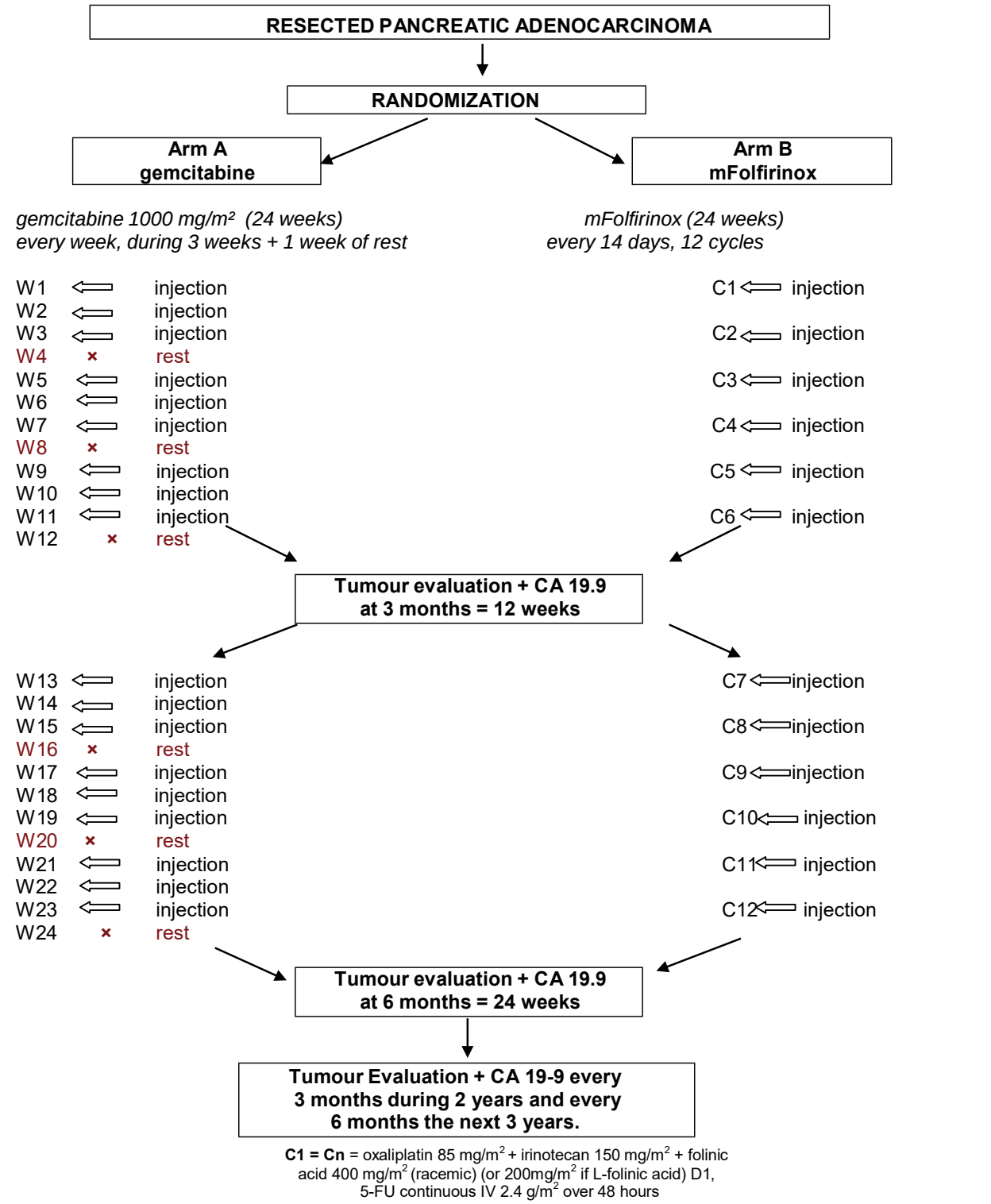
Although some studies have suggested the existence of predictive response factors (tumor size, concomitant chemotherapy) the biological factors determining tumor response are in fact unknown.
The aim of the biological study is to identify within the framework of this randomized prospective study, using genomics, the biological factors predictive of the tumor response, toxicity and early metastatic risk.

The study will be carried out in the centers willing to participate in it.

Patients who wish to participate in the biological study will receive a **second information letter** from the clinical investigator and will have to **sign a second consent form**.

3.2 Research Methodology

The trial is a biomedical, nationwide, multicenter, randomized phase III study, comparing 6-month adjuvant chemotherapy with gemcitabine versus the association 5-fluoruracil, irinotecan and oxaliplatin (mFolfirinox) in patients with resected pancreatic adenocarcinoma.


RESECTED PANCREATIC ADENOCARCINOMA
RANDOMIZATION
Arm A
gemcitabine
Arm B
mFolfirinox
gemcitabine 1000 mg/m² (24 weeks)
every week, during 3 weeks + 1 week of rest
mFolfirinox (24 weeks)
every 14 days, 12 cycles
W1 ⇦ injection
W2 ⇦ injection
W3 ⇦ injection
W4 × rest
W5 ⇦ injection
W6 ⇦ injection
W7 ⇦ injection
W8 × rest
W9 ⇦ injection
W10 ⇦ injection
W11 ⇦ injection
W12 × rest
C1 ⇦ injection
C2 ⇦ injection
C3 ⇦ injection
C4 ⇦ injection
C5 ⇦ injection
C6 ⇦ injection
Tumour evaluation + CA 19.9
at 3 months = 12 weeks
W13 ⇦ injection
W14 ⇦ injection
W15 ⇦ injection
W16 × rest
W17 ⇦ injection
W18 ⇦ injection
W19 ⇦ injection
W20 × rest
W21 ⇦ injection
W22 ⇦ injection
W23 ⇦ injection
W24 × rest
C7 ⇦ injection
C8 ⇦ injection
C9 ⇦ injection
C10 ⇦ injection
C11 ⇦ injection
C12 ⇦ injection
Tumour evaluation + CA 19.9
at 6 months = 24 weeks
Tumour Evaluation + CA 19-9 every
3 months during 2 years and every
6 months the next 3 years.
C1 = Cn = oxaliplatin 85 mg/m² + irinotecan 150 mg/m² + folinic acid 400 mg/m² (racemic) (or 200mg/m² if L-folinic acid) D1, 5-FU continuous IV 2.4 g/m² over 48 hours
The maximum treatment duration will be 6 months.

3.3 Inclusion and randomization

After patients have signed the information letter and consent form as well as the forms validating the examinations required for the baseline assessment, eligible patients will be randomized.

Randomization will be performed via internet using Tenalea, a dedicated webservice available at: https://fr.tenalea.net/valdaurel/

A user guide explaining precisely how to connect the web server and proceed to a patient's randomization will be handed out to the clinical investigators every time the trial is set up in a new center. Access to the service will be secured with an individual password required for each user.
In case of problems, or when the Internet site is unreachable, the clinical investigator will have the possibility to contact directly the randomization center directly by telephone or to FAX the randomization request form provided in the investigator's folder, duly completed and signed to:

Sophie GOURGOU-BOURGADE
Institut Régional du Cancer de Montpellier / Val d'Aurelle - Unité de Biostatistique
Monday to Friday from 9 a.m. to 9 p.m.
Fax : +33 (0)4 67 61 37 18 Tel : +33 (0)4 67 61 31 61

Once the randomization is performed by the study investigator, notification will be automatically sent by e-mail in .pdf format to:
- the investigator,
- the sponsor UNICANCER via R&D UNICANCER.
- Institut Régional du Cancer de Montpellier / Val d'Aurelle (Montpellier),

If the request is sent by Fax, the investigator will be also notified of the request by return fax.
Randomization will be stratified by the following factors:

- center
- lymph node status pN0 (< 12 lymph node examined versus ≥12 lymph node examined) versus pN1
- R0 versus R1*
- CA19-9 at inclusion ≤ 90 U/ml versus CA19-9 between 91 and 180 U/ml

*** Staining the resection margins, in particular the retroperitoneal margin (or medial margin, see appendix 3) is highly recommended.**

R1 is defined as a margin ≤ 1 mm (www.rcpath.org), except for the anterior face of the pancreas that can be considered as a true margin.
The collaboration between the surgeon and the anatomo-pathologist and between the surgeon and the chemotherapist must be organized by each participating center.

Treatment must begin within the 7 days following randomization.

3.4 Study work flow

Included patients will participate in the research protocol for the total duration of 5.5 years including 24 weeks of treatment and a follow-up of 5 years.

The investigation schedule is defined in the summary table (Paragraph H, synopsis page 8).

3.5 Early trial termination/Stopping rules and patient premature exit

3.5.1 *Temporary interruption and definitive termination of the study*

The study can be suspended or stopped by the sponsor after meeting with the principal investigator or under the request of the competent authority and/or the Committee for the Protection of Patients (CPP) for the following reasons:

- high frequency and/or unexpected severity of toxicity,
- insufficient patient enrollment,
- insufficient quality of data collection.

3.5.2 *Premature trial exit*

Premature trial exit will be exceptional and due to the following reasons:

- consent withdrawal,
- lost to follow-up,
- other : exceptional , to be specified by investigator

Patients participating in this research protocol may withdraw their consent and exit the trial at any time without justification irrespective of their reason(s). However, withdrawal of consent does not preclude the patient's right to receive treatment.

4. PATIENT SELECTION

4.1 Inclusion criteria

1. Histologically proven pancreatic ductal adenocarcinoma. Intraductal papillary mucinous tumors of the pancreas (IPMT) with invasive components are eligible.
2. Macroscopically complete resection (R0 or R1 resection).
3. Patients aged from 18 to 79 years.
4. WHO performance status 0-1.
5. No prior radiotherapy and no previous chemotherapy.
6. Full recovery from surgery and patient able to receive chemotherapy: adequate oral nutrition of ≥ 1500 calories per day and free of significant nausea and vomiting
7. Adequate hematologic function (Absolute neutrophil count ANC ≥ 1,500 cells/mm^3, platelets ≥ 100 000 cells/mm^3 and hemoglobin ≥ 10 g/L - possibly after transfusion -).
8. Serum total bilirubin ≤ 1.5 times the institutional upper limit of normal.
9. Creatinine Clearance ≥ 50 mL/min
10. Patient of child-bearing potential (for female patient: study entry after a menstrual period and a negative pregnancy test) must agree to use two medically acceptable methods of contraception (one for the patient and one for the partner) during the study and for 4 months after the last study treatment intake for women and 6 months for men..
11. Interval since surgery between 21 and 84 days
12. Patient information and signed informed consent.
13. Public or private health insurance coverage

NON INCLUSION CRITERIA

One of the following criteria is sufficient for non inclusion:

1. Other types of non-ductal tumor of the pancreas, including endocrine tumors or acinar cell adenocarcinoma, cystadenocarcinoma and ampullary carcinoma.
2. Metastases (including ascites or malignant pleural effusion).
3. Macroscopic incomplete tumor removal (R2 resection).
4. CA 19-9> 180 U / ml within 21 days of registration on study.
5. No heart failure or coronary heart disease symptoms
6. No major comorbidity that may preclude the delivery of treatment or active infection (HIV or chronic hepatitis B or C) or uncontrolled diabetes.
7. Pre-existing neuropathy, Gilbert's disease or genotype UGT1A1 * 28 / * 28.
8. Inflammatory disease of the colon or rectum, or occlusion or sub-occlusion of the intestine or severe postoperative uncontrolled diarrhea

9. Concomitant occurrence of another cancer, or history of cancer except in situ carcinoma of the cervix treated or basal cell carcinoma or squamous cell carcinoma.
10. Fructose intolerance.
11. Persons deprived of liberty or under guardianship.
12. Psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule.

5. TREATMENTS

5.1 Investigational treatments

After randomization, patients will be allocated accordingly to receive either treatment A (gemcitabine) or treatment B (mFolfirinox):

Arm A: *Gemcitabine*

Gemcitabine 1000 mg/m² IV infusion over 30 minutes, weekly, during 3 weeks + 1 week of rest (= 1 cycle) repeated 6 times (i.e., 6 cycles) during 24 weeks (overall treatment duration = 24 weeks).

Arm B: mFolfirinox.

mFolfirinox every 14 days, 12 cycles, 24 weeks, new cycle beginning on D15.

mFolfirinox :
- oxaliplatin (Eloxatin®) 85 mg/m² on D1, IV infusion over 2 hours , followed by
- irinotecan (Campto®) 150 mg/m² on D1, IV infusion over 90 minutes to begin 30 min after folinic acid infusion is started;
- folinic acid 400 mg/m² (racemic mixture) (or 200 mg/m² if L-folinic acid) IV infusion over 2 hours
- 5-FU 2.4 g/m²/h IV continuous infusion over 46 hours (1200 mg/m²/ day)

In case of delayed cycle, G-CSF support will be used when before the treatment cycle is resumed and before all remaining cycles.

The investigational products will be prepared according to the chemotherapy safety standards and the modalities described in appendix 8.

Treatment products will be supplied from the pharmacy stocks of the each research institution/hospital.

Traceability for all investigational products used in the framework of this clinical study must be maintained throughout the overall trial duration.

5.2 Treatment schedule

5.2.1 Arm A: gemcitabine (un cycle = 4 semaines de traitement)

Gemcitabine will be administered at the dose of 1000mg/m^2 injected over 30 minutes via intravenous infusion, strictly. It can be delivered on an outpatient basis (day hospital) but not at the patient's home.

The administration of gemcitabine must be repeated **once a week for 3 consecutive weeks** (Days 1, 8 and 15 of a cycle)**, followed by one week of rest** (1 cycle = 28 days). Doses will be adapted before each administration of chemotherapy, according to the individual patient tolerance to gemcitabine and weight.

The treatment with gemcitabine will continue for 24 weeks (6 cycles).

5.2.2 *Arm B : mFolfirinox: oxaliplatin + irinotecan + folinic acid + 5 fluorouracil*

Treatment will start with oxaliplatin administration at the dose of 85 mg/m^2 IV infusion over 2 hours, followed by the simultaneous administration (using a Y-tubing) of folinic acid 400 mg/m^2 (racemic) (or 200mg/m² if L-folinic acid) IV in fusion over 2 hours and irinotecan 150 mg/m^2 IV infusion over 90 min. that shall begin 30 min. after folinic acid infusion is started.
5-FU IV 2.4 g/m² will be administered through continuous infusion over 46 hours after the end of the folinic acid infusion, i.e.: 1200 mg/m^2/day for the duration of 2 days.

The next cycle starts on D15. Each cycle will be delivered every 2 weeks. The treatment can be delivered on an outpatient basis (day hospital) but not at the patient's home.

Treatment will be continued during 24 weeks (12 cycles).

General instructions

- All toxicities must be reversed before treatment can be resumed.
- Platelets must be ≥100,000 platelets/mm^3 and PNN ≥1,500/mm^3 before a treatment course starts.
- If Neutrophils <1500/mm^3 or platelets <100.000/mm^3, the treatment course must be postponed until values are reversed to neutrophils ≥ 1500/mm^3 and platelets ≥ 100000/mm^3 with G-CSF support: Granulocyte 34® (263 µg/d) (appendix 9) mandatory for all remaining cycles.
- Prevent the risk of *severe vomiting* on D1 with ondansetron + aprepitant (+ corticoids if no diabetes).
  Reduce the dose of corticoids with aprepitant :
  - the dose **dexamethasone IV and *by mouth* must be reduced by 50%.**
  - the dose **methylprednisolone IV and *by mouth* must be reduced by 25%**
    (Aapro MS, Walko CM Annals of oncology 2010)

- Prevent(delay) the risk of *vomiting* with aprepitant (plus corticoids if no diabetes).
- In the case of cholinergic syndrome under irinotecan, administer 0.25mg of atropine injected subcutaneously (SC) except in case of contra-indication.
-
- In case of history of laryngeal pseudo-spasm :
  - administer a tranquilizer before the next oxaliplatin infusion
  - hospitalization is preferable
  - prolong the infusion duration to 6 h
  - administer calcium gluconate and magnesium sulfate (if not already administered).
- Use a total sun protection cream in case of sun exposure.
- Give instructions to the patient in case of diarrhea after Campto® as well as a written document with a prescription in advance for loperamide which the patients must have at their disposal right after the first course of treatment.
- Drug Interactions: warfarin interaction with Folfox and aprepitant. Aprepitant is an inducer of cytochrome CYP2C9 which makes oral contraceptives inefficient. Therefore, another means of contraception is necessary for non-menopausal patients. Pimozide (Orap®) and cisapride (Repulsed®) are strictly contra-indicated due to a major risk of ventricular rhythm disorder, notably twisting spikes (i.e. torsades de pointes).
- Advise the prescription of pancreatic extracts to limit the risk of diarrhea.

5.3 Dose adaptation and measures to take in case of toxicity.

In the case a dose reduction is necessary; the reduced posology (dosage) will be maintained until the end of treatment.
In case of recurrent grade 4 toxicity despite dose reduction, the clinical investigator and the patient may discuss the possibility of stopping the treatment.

PATIENTS SHALL NEVER EXIT THE STUDY
IN ANY SITUATION THEY WILL BE MONITORED AFTER CHEMOTHERAPY

5.3.1 Measures in case of hematological toxicity

ARM A: GEMCITABINE

CBC before each administration	CYCLE DELAY	DOSE REDUCTION
PNN > 1 x 10^9 /l **and** platelets > 100 x 10^9 /l	no cycle delay	Administer 100 % of the total dose
0.5 < PNN ≤ 1 x 10^9 /l **or** 50 < platelets ≤100 x 10^9 /l	no cycle delay	Administer 75 % of the total dose (dose reduction 25%)
PNN ≤ 0.5 x 10^9 /l **or** platelets ≤ 50 x10^9 /l	Course delayed until values are reverted back to 0.5 x 10^9/l (PNN) and 50 x10^9/l (platelets)	No dose reduction

PNN: polynuclear neutrophils

ARM B: **mFOLFIRINOX**

CBC on D15	CYCLE DELAY	DOSE REDUCTION		
		Irinotecan (CPT-11)	**Oxaliplatin (L-OHP)**	**LV5FU****
PNN ≥ 1.5 x 10^9 /l and plat. ≥ 100x10^9 /l	No cycle delay	no dose reduction		
PNN < 1.5 x 10^9 /l	Treatment delayed until PNN ≥ 1.5 x 10^9/l (until D22 or D29 if necessary) and resume cycle with G-CSF. In case of no recovery on D29, discuss treatment stop, C-GSF, or maintain only LV5FU **	1st episode : dose reduction to 120 mg/m² 2nd episode : maintain dose at 120 mg/m² 3rd episode : discuss treatment stop or maintain only LV5FU * *	1st episode : no dose reduction 2nd episode : reduce dose to 60 mg/m² 3rd episode : discuss treatment stop or maintain only LV5FU **	**1st episode** : no dose reduction
Plat. < 100x10^9 /l	Delay treatment until recovery (plat. ≥ 100 x10^9/l). If no recovery on D29, discuss **treatment stop***	1st episode : no reduction in dose 2nd episode : reduce dose to 120 mg/m² 3rd episode : discuss stopping treatment*	1st episode : reduce dose to 60 mg/m² 2nd episode : maintain dose at 60 mg/m² 3rd episode : discuss **oxaliplatin stop***	**1st episode** : no dose reduction **2nd episode** : reduce the dose of IV continue infusion by 25%

* *To be discussed between the patient and the clinical investigator. The use of prophylactic G-CSF is advised automatically when there is cycle delayed due to hematologic toxicity involving PNN and lasting at least one week. To be evaluated on a case to case basis, if necessary with the principal investigator in function of the rapport benefit/risk ratio and the number of administered courses.*

*** LV5FU = folinic acid + continuous infusion -FU*

5.3.2 Measures in case of hematological toxicity during the inter-cycle interval (nadir) in the mFolfirinox arm

EVENTS	DOSE REDUCTION
-Febrile neutropenia* isolated -Grade 4 neutropenia > 7 days -Infection with concomitant grade 3-4 neutropenia	**1st episode**: reduce irinotecan dose to 120 mg/m^2 plus G-CSF **2nd episode**: in addition reduce oxaliplatin dose to 60 mg/m^2 **3rd episode**: discuss growth factor or further treatment reduction, maintain only LV5FU if necessary.
Thrombocytopenia, grade 3-4	**1st episode** : reduce the dose of oxaliplatin to 60 mg/m^2 **2nd episode** : in addition reduce the irinotecan dose to 120 mg/m^2 and reduce 5-FU IV continuous by 25 % **3rd episode** : **stop oxaliplatin and irinotecan, continue LV5FU**

***Definition**: occurring during a period of medullar hypoplasia (PNN <500/mm^3) with fever > 38.5°C.
Treatment will be continued with the same doses, but with adjunction of G-CSF for all the remaining cycles: Granocyte 34® (263 µg/d) (appendix 9) from D5 to D10. The first dose must not be administered within the 24 hours following the end of the cytotoxic chemotherapy.

5.3.3 Measures in case of digestive toxicities in the mFolfirinox arm

EVENTS	DOSE REDUCTION
-Isolated grade **3-4** diarrhea or -Diarrhea + fever and/or grade 3-4 neutropenia	**1st episode** : reduce irinotecan to 120 mg/m^2 **2nd episode** : reduce oxaliplatin to 60 mg/m^2 and reduce 5-FU continue by 25 % **3rd episode** : **stop irinotecan**
Recurrent diarrhea (> 48 h) despite high doses of loperamide	No dose reduction for irinotecan, oxaliplatin and 5-FU after recovery except if grade 3-4 diarrhea, or diarrhea + fever and/or grade 3-4 neutropenia

In case of occurrence of gastrointestinal ulceration hemorrhagic or not, treatment with 5-fluorouracil should be stopped until disappearance of the symptoms

5.3.4 Pulmonary toxicity

In patients with pulmonary interstitial disease risk factors, the occurrence of respiratory symptoms will be closely monitored before and during treatment.

5.3.5 In case of hepatic toxicity in the gemcitabine arm.

Frequent increase of hepatic transaminases is observed.

- If the transaminases (ALT or AST or both) increase is less than 5 X ULN, gemcitabine will be continued without dose reduction.
- If the transaminases (ALT or AST or both) increase is more than 5 to 20 X ULN, gemcitabine must be reduced by 25%
- If the transaminases (ALT or AST or both) increase is more than 20 X ULN, gemcitabine must be definitely stopped.

ULN: upper limit of normal

5.3.6 In case of mucositis or hand-foot syndrome in the mFolfirinox arm

These toxicities are caused by 5-FU.
If grade 3-4 toxicity occurs, continuous 5-FU IV infusion will be reduced by 25% for the remaining courses.

5.3.7 In case of cardiac toxicity

In case of angina pectoris or myocardial infarction, 5-FU treatment shall be stopped. The reintroduction of 5-fluorouracil is not allowed.

5.3.8 Peripheral neuropathy

The dose of oxaliplatin can be adapted according to the following table:

Toxicity	Duration of toxicity		
	≤ 7 days	**> 7 days and < 14 days**	**Persisting between cycles**
Paresthesia/dysesthesia without functional alteration (grade 1 NCI)	no modification	no modification	no modification
Paresthesia/dysesthesia with functional alteration not impacting activities of daily living (grade 2 NCI)	no modification	no modification	**65 mg/m^2**
Paresthesia/dysesthesia with pain or functional alteration impacting activities of daily living (grade 3 NCI)	**65 mg/m^2**	**65 mg/m^2**	stop
Persistent paresthesia/dysesthesia, incapacitating	NA	NA	stop
Acute laryngopharyngeal dysesthesia	Prolong infusion duration to 6 hours. Add (if it is not already the case) 1g of calcium gluconate and 1g of magnesium sulfate over 15 min. before the oxaliplatin infusion, action to be repeated again after the oxaliplatin infusion		

If oxaliplatin is stopped because of neurotoxicity, irinotecan and 5-FU should be continued.

5.3.9 Dose adaptation in case of bilirubin elevation

If bilirubin increase is >1.5 ULN, it is preferable to postpone chemotherapy, because irinotecan is eliminated via the gallbladder, and check the presence of a tumour relapse or obstruction of biliary anastomosis. Indication of chemotherapy will be retained if these two diagnoses are eliminated. However, it will be preferable to stop irinotecan if bilirubin elevation is persistent.

5.3.10 Other toxicities

Other toxicities with ε grade 2, except anemia and alopecia, may justify a dose reduction of 25%,
If it is medically indicated, for instance, reduction of irinotecan to 120 mg/m^2 and/or oxaliplatin to 60 mg/m^2 and/or 5-FU decreased by 25 % in function of the type of toxicity.

5.4 Symptomatic treatment of toxicities

5.4.1 Cholinergic syndrome

In case of acute cholinergic syndrome (sweating, increased saliva, visual disorder, lacrimation, mitosis, abdominal cramping, early diarrhea) subcutaneous atropine 0.25 mg will be injected curatively (except if there are contraindications: closed-angle glaucoma, severe dysuria or prostatic hypertrophy) and thereafter preventively for the next courses, except if there is a contraindication for patients treated with irinotecan.

5.4.2 Late diarrhea

Prophylactic treatment:

No prophylactic treatment must be prescribed; in particular, loperamide shall not be administered prophylactically. However, the patients must stop any treatment with laxative and avoid aliments/nutrients and drinks known to accelerate the intestinal transit.

Curative treatment:

- From 1st soft or liquid stool the patient must take 2 capsules of loperamide (by mouth immediately and thereafter 1 capsule every 2 hours until at least 12 h after the last liquid stool, without exceeding an overall treatment duration of 48 h. Electrolyte replacement drinks will be indicated during the whole diarrhea episode.

- If diarrhea persists more than 48 h despite the recommended treatment with loperamide, broad-spectrum antibiotics (fluoroquinolone) will be prescribed, systematically for a 7-day period, after medical consultation.

- In case of persistent and/or severe diarrhea, the patient will be hospitalized and rehydrated parenterally. Loperamide will be replaced by another antidiarrheal treatment left to the clinical investigator's choice. Eliminate the possibility of pseudomembranous colitis if diarrhea persists.

- Oral antibiotic therapy with fluoroquinolone must also be prescribed in case of grade 4 diarrhea or diarrhea associated to a grade 3-4 neutropenia or fever.

- Patients with vomiting or fever or with a performance status > 2 concomitant to diarrhea will be rapidly hospitalized to receive parenteral support. Loperamide and fluoroquinolone must be prescribed to the patient in advance upon exiting the hospital so that he/she has both medications with him/her if diarrhea reoccurs.

5.4.3 Nausea and vomiting

Before oxaliplatin administration, an association of corticoids (30 minutes before), anti 5HT3 (ondansetron) 15 min. before and aprepitant (Emend®) is recommended.

- The dose of corticoids must be reduced with aprepitant:
  - The dose of dexamethasone, IV and oral, reduced by 50%.
  - The dose of methylprednisolone, IV and oral, reduced by 25% (Aapro MS, Walko CM Annals of oncology 2010)

Preventing nausea and delayed vomiting is also recommended, using for instance aprepitant and corticoids.

WARNING: In case of diabetes, corticoids must be used with very high precaution.

5.4.4 Neutropenia

In case of severe neutropenia (grade 3-4) patients have a high risk of developing febrile neutropenia and infection, notably in the case of concomitant diarrhea. If these symptoms appear, posology adaptations are planned for the next cycle (see section 5.3.1).

Administration of hematopoietic growth factor is not recommended in the 1st cycle; however, they can be indicated on a case by case basis according to the clinical status of the patient. When the use of a G-CSF is necessary, a treatment with Granocyte 34® (263 µg/j) (appendix 9) is advised from D5 to D10.

5.4.5 Anemia

In case of anemia (e.g. hemoglobin ≤ 11 g/dl), transfusions or treatment with erythropoietin will be started, at the clinician discretion.
Since an increased frequency of thromboembolic accidents was observed in some patients treated with erythropoietin, notably when hemoglobin was > 13 g/dl, complete blood count monitoring will be reinforced. Moreover, as it is the case with other growth factors, the risk of tumor growth cannot be totally excluded with erythropoietin.

5.4.6 Extravasation

Severe reactions due to irinotecan or oxaliplatin extravasation have been reported (Kretzschmar A et al. 2010).
General recommendations in case of extravasation are as follow:
- stop infusion immediately,
- do not remove the needle or the catheter,
- suck/aspirate the maximum of infiltrated product through the needle,
- apply ice on the infiltrated area for 15 to 20 minutes every 4 to 6 hours for a period of 72 h,
- apply local corticotherapy,
- check regularly the infiltrated site during the following days, to verify whether more treatment is needed. Do not hesitate to require a surgical consultation in case of doubt.

5.4.7 Alopecia

The use of a refrigerating helmet to prevent hair loss is efficient with Campto®, but the prior administration of oxaliplatin will increase the intolerance to cold.

5.5 Treatment stop

The investigator may prematurely interrupt the treatment for any reason in the best interest of the patient, including concomitant disease or adverse event.
In case of premature treatment stop, irrespective of the moment or reason, the investigator must document the reasons as exhaustively as possible.
Patient monitoring will continue in accordance with the protocol and follow-up data will be collected until the end of the study.

5.6 Concomitant treatments

5.6.1 Authorized medications

All symptomatic treatment necessary to the patients' comfort (antiemetics, antidiarrheals) are authorized and their type, posology and duration of administration, as well as all other medically justified treatments are authorized.

Aprepitant is an inducer of cytochrome CYP2C9 which inactivates all oral contraceptives. Another means of contraception is therefore necessary for non-menopausal patients.

5.6.2 Contraindicated medications

Other antitumor treatments (chemotherapy, hormonal therapy, biological response modifier, targeted therapy) must not be used.
Corticoids are forbidden except in case of urgent indication or as antiemetics. Their use will require the highest precaution in patients with diabetes.

It is advised not to use the association of warfarin (Coumadin®) with mFOLFIRINOX. It is preferable to use heparin and therapeutic anticoagulation with low-molecular weight heparin. If warfarin cannot be avoided, the rate of prothrombin must be checked more frequently and INR monitored.

Pimozide (Orap®) and cisapride (Prepulsid®) are strictly contraindicated: they are associated with a major risk of disorder of the ventricular rhythm (notably twisting spikes i.e. torsades de pointes).

Yellow fever vaccine

5.6.3 Main medications that can interact with irinotecan

- Concomitant treatments based on St John's wort (alternative medicine) are absolutely contraindicated with irinotecan (Campto®); this plant decreases the serum concentration of SN-38, the active metabolite of irinotecan.

- CYP3A4 inhibitors such as cimetidine, macrolide antibiotics (azithromycin, clarithromycin, erythromycin), azolated antifungal agents (fluconazole, ketoconazole, itraconazole), grapefruit juice, and the calcium channel blockers that inhibit CYP3A4 (verapamil, diltiazem, nifedipine)) could increase the irinotecan toxicity. This type of interaction was observed in cancer patients receiving concomitantly irinotecan and ketoconazole, a powerful inhibitor of CYP3A4.
- Exposure to fluoroquinolones, such as ciprofloxacine or norfloxacine, can be enhanced in patients with altered renal function subsequent to dehydration or colorectal cancer complications. In these patients, the concomitant administration of irinotecan and antibiotics belonging to fluoroquinolone class, inhibiting CYP3A4 could increase the irinotecan toxicity.

5.6.4 Main medications that can interact with 5-FU

- Metronidazole: the concomitant administration of metronidazole can enhance toxicity of 5-FU by decreasing its clearance.
- Allopurinol (Zyloric®): concomitant administration of this product must be avoided (loss of 5-FU efficacy).

5.6.5 Main medications that can interact with oxaliplatin

There is a risk of convulsion caused by an interaction between phenytoin and oxaliplatin. Phenytoin is therefore contraindicated.

5.6.6 Main medications that can interact with gemcitabine

Gemcitabine has known drug interactions. Similarly to any chemotherapy, the antiamrile vaccine (yellow fever) and live attenuated vaccines are contra-indicated because of the risk of potentially fatal systemic involvement, notably in immunosuppressed patients.

6. BASELINE ASSESSMENT AND FOLLOW-UP

A table summarizing patient monitoring and evaluation schedule from the date of randomization till the end of the study can be found in section H of the protocol synopsis.

6.1 Baseline assessment

Eligible patients with informed signed consent will undergo a clinical examination and a biological evaluation within the 7 days preceding randomization and within a time delay of maximum 84 days after surgery.

- **Clinical examination**
  - Complete clinical examination with neurological assessment: weight, height, WHO performance status, comorbidities, current treatments.

- **Paraclinical examinations** (to be realized within maximum 30 days before randomization)
  - Electrocardiogram.
  - Post-operative thoracic-abdominal-pelvic CT scan.
  - MRI abdominal –pelvic **and** a thoracic scan (if allergic to the contrasting agent)

- **Biological tests**
  - Complete blood count (CBC) with platelets,
  - Electrolytes, glucose,
  - Alkaline phosphatase, total, free and conjugated bilirubin, AST, ALT, albumin, serum creatinine, calculated creatinine clearance,
  - Post-operative CA 19-9,
  - Pregnancy test for fertile women without contraception

- **Translational research (appendix 14)**

In order to carry out the translational research samples will be taken:

-**tumor sample**

-**blood sample** collected from a venous blood puncture performed during medical care/examination necessary for the patient. In no circumstances additional samples can be performed for the translational research. ADN will be extracted from 2 x 5 ml peripheral venous blood. Samples will be conserved in a classical refrigerator until they are sent to the translational research unit (coordinates will be pre-printed cf. Appendix 14.

During randomization each center will offer the patient the option to participate in the biological study. If the patient accepts, the type of biopsy and/or blood sample taken will be recorded/filed at the same time as randomization request.

If a blood sample is scheduled, immediately after the patient inclusion, the center will receive a shipment box for biological materials to be used for sending the 2 blood samples to the translational research laboratory.

6.2 Evaluation before each treatment

To be performed: evaluation of the WHO performance status, complete blood count (CBC), platelets count, Electrolytes, protein, glucose, free and conjugated bilirubin levels, transaminases (ALT and AST), toxicity evaluation.

Patients will be evaluated every week or every two weeks according to the treatment arm.

6.2.1 Arm A- Gemcitabine

Before each administration: every 7 days during 3 weeks + 1 week of rest, for 24 weeks
Patients treated with gemcitabine will be evaluated with a clinical examination before each administration to assess toxicities and decide whether the treatment can be continued.

- Evaluation of WHO performance (appendix 6)
- Evaluation of tolerance during the inter-cycle interval
- Verification of the recovery from toxicities to initial level or to grade ≤ 1 (except alopecia)
- CBC, platelets
- Electrolytes
- Protein
- Glucose
- Total, free and conjugated bilirubin
- Transaminases AST and ALT

6.2.2 Arm B- mFolfirinox

On D8 of the first cycle (or in case of diarrhea)

- CBC platelets, serum creatinine, potassium

Before each cycle: every 14 days

Patients treated with mFOLFIRINOX will be evaluated before each new cycle with a clinical examination to assess toxicities and whether treatment can be continued.

- Evaluation of WHO performance (appendix 6)
- Evaluation of tolerance during the inter-cycle interval
- Verification of the recovery from toxicities to initial level or to grade ≤ 1 (except alopecia)
- CBC, platelets
- Electrolytes
- Protein
- Glucose

- Total, free or conjugated bilirubin
- Transaminases AST and ALT

However, in case of intolerance, additional consultations/visits may be scheduled.

All examinations revealing toxicity related to the treatment must be repeated periodically until the toxicity is reverted (or until it is deemed irreversible).

6.3 Intermediate evaluation at 12 weeks (3 months)

- Thoracic-abdominal-pelvic CT scan
- MRI abdominal–pelvic **and** a thoracic scan (if allergic to the contrasting agent)
- Complete clinical examination including weight, WHO performance status and toxicity assessment
- Dosage of CA 19-9

6.4 End of treatment evaluation at 24 weeks (6 months)

The final evaluation will be realized within the 2 to 4 weeks following the last chemotherapy course to evaluate the absence of relapse. It includes:

- Thoracic-abdominal-pelvic CT scan
- MRI abdominal–pelvic **and** a thoracic scan (if allergic to the contrasting agent)
- Complete clinical examination with neurological examination and evaluation of weight, WHO Performance status, acute and late toxicities
- Dosage du CA 19-9

6.5 Survival evaluation

Follow-up visits will be performed every 3 months for a period of 2 years and thereafter every 6 months for a period of 3 years.

- Thoracic-abdominal-pelvic CT scan
- MRI abdominal–pelvic **and** a thoracic scan (if allergic to the contrasting agent)
- Complete clinical examination with evaluation of weight, WHO performance status and toxicities
- Dosage of CA 19-9

7. SAFETY EVALUATION

7.1 Adverse event

Adverse events (AE) are any untoward/unfavorable manifestation, affecting any patient or individual participating in a clinical trial and receiving an experimental treatment, that is not necessarily related to the experimental treatment or research protocol.

All AEs will be reported in the CRF by the physician-investigator, from the date of the patient's signed consent until 28 days after the last administration of a treatment drug.

7.2 Serious Adverse Event (SAE) definition

The following events must be considered as serious adverse event (SAEs) related or not to the experimental drugs and must be duly notified to the sponsor:

- any death,
- the patient is in a critical state,
- any hospitalization, not planned in the protocol (≥ 24h), or prolonged hospitalization,
- a clinically significant temporary or permanent invalidity or incapacitation,
- a second cancer,
- a congenital anomaly or fetal deformity or abortion,
- any significant medical event (drug overdose, adverse clinical event or severely abnormal laboratory test, or considered as such by the physician investigator).

It will be considered as medically significant: any serious adverse event the nature, the severity or the symptom evolution of which match the information described in the SPC, especially for the investigational drugs with market approval.

Any clinically significant event or laboratory test deemed serious by the clinical investigator, and not corresponding to the criteria listed above, will be considered medically important. The patient may be at risk and the situation requires medical intervention to prevent untoward outcome corresponding to an SAE (e.g.: drug overdose, second cancer, pregnancy,…).

Invalidity and incapacity corresponding to any clinically significant physical or psychological disability, temporary or permanent, impacting the patient's physical activity and/or quality of life.

The following events will not be considered serious adverse events:

- hospitalization < 24 hours,
- any surgical intervention or hospitalization planned prior to patient inclusion in the study and/or scheduled by the study protocol (biopsy, chemotherapy..).

Adverse event due to an experimental product: any untoward and unwanted reaction to an experimental product irrespective of the administered dose.

Expected serious adverse event (e-SAE): it is considered as an expected serious adverse event (e-SAE): any serious adverse event the nature, the severity or the symptom evolution of which matches the information described in the SPC, especially for the investigational drugs with market approval.

Unexpected serious adverse event (u-SAE): it is considered as an unexpected serious adverse event (u-SAE): any serious adverse event the nature, the severity or the symptom evolution of which does not match the information provided in the Investigator's Brochure (IB) regarding the investigational drug used, if it has been not approved for the market, or in the Summary of Product Characteristics (SPC) in case of the drug being approved.

Intensity criterion: the intensity of an adverse event must not be confounded with its severity that is the criterion used to determine whether it must be declared to the competent authority.

Event intensity will be estimated according to the criteria from CTC-AE version 4.0 (see Appendix 3). Intensity of adverse events not listed in this classification will be described using the following terms:

Light (grade 1): does not perturb daily life activity
Moderate (grade 2): perturbs daily life activity
Severe (grade 3): precludes usual daily life activity
Very severe (grade 4): requires intensive care/ the patient is in a critical state
Death (grade 5)

7.3 Serious adverse event reporting

U-SAEs must be collected until the end of the post-operatory period (60 days after surgery) and must be notified to the sponsor's pharmacovigilance cell **within 48 working hours** by FAX with the u-SAE form from the CRF:

Cellule de Pharmacovigilance
Bureau d'Etudes Cliniques et Thérapeutiques
Tel.: +33 (0)1 44 23 04 16 – Fax : +33 (0)1 44 23 55 70

Beyond the 60 day period, only u-SAE that might be related to the study must be notified to the sponsor.

The investigator must report without delay to the UNICANCER pharmacovigilance unit (PV-UNICANCER), any SAE occurring during the study or within a 30-day delay after the last administration of the investigational product, whether it is imputable or not to the research,

Any delayed SAE (occurring after the 30-day delay) and reasonably considered to be related to the investigational treatments or the research carried out (other treatments used, diagnosis procedures and investigations realized during the research study) must be declared without limit of time.

Immediately upon being aware of an SAE, the investigator must notify by Fax the UNICANCER Pharmacovigilance Unit using the form **"serious adverse event notification form"** that is provided in the investigator's folder, and document it as accurately and precisely as possible. The form must be dated and signed by the investigator before it is sent to:

FÉDÉRATION NATIONALE DES CENTRES DE LUTTE CONTRE LE CANCER
Unité de Pharmacovigilance
Tel.: +33 (0)1 44 23 04 16 – Fax: +33 (0)1 44 23 55 70
e-mail: pv-R&D@unicancer.fr

For each SAE, the investigator will provide:
- a clear description using the appropriate medical terminology,
- the intensity,
- the date of beginning and end,
- the measures taken and whether or not a treatment was needed,
- whether the experimental treatment was interrupted,
- the event evolution: in case of non-fatal SAE, the event evolution will be monitored until the patient has recovered her/his previous state or the sequellae are stabilized,
- the causality between the event and the investigational treatment or a constraint related to the research (period without treatment, additional examinations required within the framework of the study, etc.),
- the causality with the treated pathology, another pathology or treatment.

Whenever it is possible, the investigator must also attach to the SAE report the following items:
- a copy of hospitalization report or prolongation,
- a copy of the autopsy report if necessary,
- a copy of the results of all additional examination performed, including relevant negative results specifying the normal laboratory values,
- any other document deemed relevant.

All these documents must be made anonymous.

Additional information may be requested (by fax, e-mail, telephone or during a visit) by the study monitor and/or by the UNICANCER Pharmacovigilance via a Data Correction Form (DCF).

Any expected adverse event the intensity, evolution or frequency of which may differ from what is reasonably expected, will be considered as unexpected by the pharmacovigilance unit.
A list of expected SAEs, based on the investigational products SPCs is provided and is attached to the protocol (appendix 13).

Last SPC updates for each investigational product will be provided in the investigator folder.

7.4 Follow-up modalities and durations after a serious adverse event

The clinical investigator is responsible for the setup of adequate follow-up until the affected patients have returned to their previous state or until the toxicity is reverted or stabilized, or until the patient's death. Sometimes, this may imply that the follow-up is prolonged after the patient has exited the trial.

Immediately upon being aware of this information, the clinical investigator is to send additional information to the UNICANCER Pharmacovigilance unit via a SAE declaration form (ticking the box 'Following n° X' to specify it is about an event follow-up and not an initial event). He/she must also send the last follow-up form when the SAE is reversed or stabilized.

The clinical investigator archives all the documents concerning presumed SAEs to allow complementary information to be communicated if necessary.

The clinical investigator responds to any request from the UNICANCER Pharmacovigilance unit to document the initial observation.

8. BIOLOGICAL STUDY

Although some studies have suggested the existence of predictive factors of response: tumor size, concomitant chemotherapy, the biological factors determining tumor response are not known.
The objective of the biological study is to identify, within the framework of the prospective randomized clinical trial, the biological factors predictive of tumor response, toxicity and the metastatic risk (with genomics).

This study of biological factors which are predictive of the response to treatment will be undertaken by centers willing to participate.

Patients willing to participate in the biological study will receive a **specific letter of information** from the clinical investigator and signed a **second informed consent form**.

9. STATISTICAL PLAN

9.1 Sample size

PRODIGE/ACCORD 24 is a superiority trial evaluating 2 treatment groups: (1) the standard treatment with gemcitabine (control arm) versus (2) mFolfirinox polychemotherapy (experimental arm). The total number of randomized patients will be 490.

Similarly to the CONKO-001 trial that has validated the use of gemcitabine as adjuvant treatment, **disease-free survival** is the primary objective of this study because it provides an earlier evaluation of the possible gain of efficacy compared with the evaluation of the overall survival (OS) that requires longer follow-up. In addition, there is a number of reasons to justify the choice of DFS instead of OS. Assessing DFS also confers an advantage in terms of feasibility because it requires a number of patient inclusions considerably smaller than for OS. Moreover, evaluating DFS avoids the OS results bias due to the fact that quite a number patients switch to mFolfirinox; a situation that is likely to occur for patients who relapse under treatment with adjuvant gemcitabine. Finally, DFS can be considered to be a surrogate endpoint (Fleming's type 2 criterion) for OS because relapsing pancreatic cancer is incurable today and because all the adjuvant chemotherapy studies carried out on this disease yield overall and disease-free survival curves that are proportional to each other (with parallel slopes).

Required number of patients
With a bilateral alpha risk = 0.05 and 80% power, it is necessary to observe of **342 events** to demonstrate a **median survival benefit between 14 and 19 months** corresponding to a **hazard ratio HR=0.74 and a 10% increase in the DFS at 3 years (from 17% to 27%)**. This implies that 490 patients in total (245 in each arm) must be included. Considering an accrual rate of 150 patients per year, the period of inclusion should extend over 3.5 to 4 years.

9.2 Statistical analysis

A detailed statistical analysis plan (SAP) will be elaborated before the I/O on the database is frozen for the interim analysis.

All statistical analyses will be performed on an intent-to-treat (ITT) basis. Tolerance will be assessed in patients who have received at least one administration of one of the study drugs.

Qualitative variables will be presented using:

- frequencies and percentages, and comparison between the treatment groups will be made with the chi-2 test;
- Quantitative variables will be presented using average value, standard deviation, median value and range. Comparison between treatment groups will be made with the Student T-test or the Kruskal-Wallis

test according to the case. Toxicity grades will be compared with the non- parametric test of Kruskal-Wallis.

- Disease-free survival will be defined as the time between patient randomization and first event occurrence such as local relapse, metastatic relapse, second cancer or death from any cause.
- DFS and OS curves will be estimated with the Kaplan-Meier method and survival estimates at 1, 2 and 3 years will be calculated with their associated CI95% confidence intervals.
- The effect of the experimental treatment relative to the control arm will be presented with its hazard ratio and CI95% confidence interval. The statistical test will be stratified.
- Prognostic factors for disease recurrence will be evaluated with the Cox proportional hazard model.

All statistical analyses will be performed with the Stata v10 software.

9.3 Interim analysis and trial monitoring

An early tolerance analysis is planned after the first 30 patients included have received two 2 cycles of treatment to ascertain that the rate of grade 3-4 diarrhea does not exceed 5%. Otherwise, the dose of irinotecan will be reduced to 150 mg/m^2.

An interim analysis is scheduled for the main criterion after 1/3 of the expected events, i.e.113 first events, are observed. The interim analysis, performed according to the O'Brien-Fleming design, will allow us to reject either the null hypothesis if $p \leq 0.0002$ and conclude to the superiority of the experimental treatment, or the alternative hypothesis if $p \geq 0.97$ and conclude to the non-superiority of the experimental treatment.

The interim analysis will be carried out about 2 years after the beginning of inclusions that is to say after the first 300 patients have been included.

Calculations for the interim analysis were made with the East 5 (v5.3.1.0) software.

9.4 Stopping rules and early trial termination based on toxic deaths

The rate of toxic deaths in the experimental arm will be carefully monitored. Based on this criterion, rules for stopping the trial early will be defined according to the sequential method devised by A Kramar and C Bascoul-Mollevi (2009) who recommend to stop inclusion **if the rate of toxic deaths is significantly higher than 2%** with nominal parameters $\alpha = 10\%$ and $\gamma = 4$ for the inclusion of the planned 245 patients.

The following table summarizes the set of rules to be applied from the observation of the 2nd and up to the 5th toxic death:

Number of observed toxic deaths leading to inclusion stop	*Number of patients included in the experimental arm*
2	*9*
3	*35*
4	*61*
5	*88*

It is recommended to stop the inclusions if the 2nd toxic death occurs among the first 9 patients included, the 3rd toxic death occurs among the first 35 patients, the 4th toxic death occurs among the first 61 patients or the 5th toxic death occurs among the first 88 premiers patients. Beyond the 2nd toxic death, irrespective of the number of patients included, the Independent Data Monitoring Committee will meet to decide whether the study can be continued and discuss the modalities of continuation.

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A parallel monitoring will be organized with the pharmacovigilance unit of UNICANCER to alert the principal investigator, the trial's statistician and the sponsor in case of unexpected death and communicate any SAE.

Based on the data available from the trial and other sources of information, the IDMC committee will propose the trial early termination if it is deemed necessary and if evidences are sufficiently relevant to influence the therapeutic practice of a majority of physicians.

9.5 Study population

All statistical analyses will be performed on an intent-to-treat basis (ITT), that is to say that all the randomized patients will be taken into account in the statistical analysis according to their randomization group.

Populations for analysis are defined as follows :

- ITT = all randomized patients analyzed in their randomization arm.
- ITT modified = population eligible for ITT (patients presenting a major deviation from the inclusion/exclusion criteria will not be selected).

9.6 Modifications of the statistical analysis plan and initial strategy

Any modification to the initial statistical analysis plan (PAS) will be detailed with all the necessary arguments reported in an updated version of PAS. These modifications can include supplementary or exploratory analyses that were not initially planned.

10. QUALITY CONTROL AND QUALITY ASSURANCE

10.1 Monitoring committee

10.1.1 Independent Data Monitoring Committee (IDMC)

An Independent Data Monitoring Committee (IDMC) will be set up to guarantee effective protection of patients, insure the ethical conduct of the trial, evaluate the benefit/risk ratio, and supervise the review of the scientific results during and at the end of the trial.

The IDMC committee will meet to analyze the digestive toxicity for the first 2 cycles after the first 30 patients are included. If more than 5% of patients are affected by grade 3-4 diarrhea the dose of irinotecan will be decreased to 150 mg/m^2.

The committee will be informed without delay of any toxic death and will meet when the 2nd toxic death is observed to decide whether the trial must be stopped according to the statistical rules defined in the protocol (see section 9.4).

The committee will meet after the first 113 events are observed (corresponding to about 300 included patients), after database I/O has been stopped and the interim analysis performed, to evaluate the treatment efficacy and toxicity profile. The committee will consist of at least 3 members:
- a medical oncologist
- a surgeon
- a trial methodologist

The interim analysis will be presented to the committee.

The committee may recommend the early termination of the trial if one of the following conditions is fulfilled:

- the results of the interim analysis clearly show that the experimental treatment is either superior ($p<0.0002$) or not superior ($p>0.97$) to the reference treatment,

- unacceptable toxicity (see paragraph 7.4),

- all available data from the trial or any other source of information are sufficiently convincing to influence the therapeutical practices of the majority of clinicians.

The committee has only a consultative role; it will inform the Sponsor who will decide whether the IDMC recommendation will be followed.

10.2 Quality assurance

10.2.1 Data collection

Submission of all data necessary to the research must be stated in the trial case report forms (CRFs). CRFs will be completed by the clinical investigator or another designated member from his/her staff.
Inputs in CRFs must be made with a ballpoint pen (not a pencil) and must be clearly legible. Correction pen or fluid cannot be used.
Necessary corrections will be made by the investigator or a designated member of his/her staff as follows: the erroneous data must be crossed out but should remain legible, and the correct input written nearby, dated and signed, by the person correcting it.

The following data will be collected:
- Clinical examination, weight, height, vital signs
- Blood and biological test
- Adverse events and serious adverse events occurring at each cycle

During the trial, data correction request (DCFs) may be sent by the data-management unit (*Unité de Biostatistique de l'* Institut Régional du Cancer de Montpellier / Val d'Aurelle*)* for data consistency validation. These forms must completed by the authorized persons the same way as the CRFs.

10.2.2 Research Monitoring

To ensure data authenticity in accordance with the Good Clinical Practices (BPC of November 24, 2006), the sponsor establishes a system of quality assurance that consists of:

- managing the trial monitoring according to the UNICANCER procedure,
- data quality control (for all data from participating centers) with:
  - verifying that the protocol, as well as the Good Clinical Practices, the laws and regulations currently in force are accurately followed,
  - verifying the consent and eligibility of each patient participating in the research,
  - verifying the CRF data are consistent and in agreement with the source documents,
  - verifying the notification of each SAE,
  - verifying the drug traceability (distribution, storage and accountability),
  - verifying, if applicable, that patients are not already participating in another research study which may exclude their inclusion in the research offered by the protocol.
- auditing the participating centers when deemed necessary,

The experts in charge of research monitoring will be mandated by the sponsor. They must have access to all patient data as is necessary to their mission and are bound by professional secrecy under the regulation of the French penal code (articles 226-13 and 226-1). Written reports must be issued to ensure monitoring traceability.

The clinical investigators will commit to giving the monitoring experts and the representatives of the competent authorities direct access to all patient files.

10.2.3 Auditing

Within the framework of the auditing program, the sponsor may have to conduct the audit of some participating centers. Participating centers and clinical investigators accept to comply with the audit that the sponsor or any mandated sponsor representative may conduct during a period of 10 years following the end of the study.

Participating centers and clinical investigators commit to dedicating the time necessary to the conduct of the audit and inspection procedures, to providing additional information requested by the sponsor, the competent health authority and/or any other official authority.

11. ETHICAL AND REGULATORY ISSUES

The clinical trial must be conducted in accordance with:

- the principles of ethics as stated in the last version in use of the Declaration of Helsinki,
- the Good Clinical Practices of November 24th, 2006, defined by the International Conference on Harmonization (ICH–E6, 17/07/96),
- the European directive 2001/20/CE on the conduct of clinical trials,
- the Huriet's law (n° 88-1138) of December 20th , 1988, relative to the protection of persons participating in biomedical research and modified by the Public Health Law n°2004-806 of August 9th , 2004,
- the law on 'digital information and Freedom' (Informatique et Libertés n° 78-17) of January 6th ,1978 modified by the law n° 2004-801 of August 6th, 2004 relative to the protection of persons with regard to the computerized processing of personal data,
- the bioethics law n° 2004-800 of August 6th, 2004.

11.1 Ethics Committee/Committee for the Protection of Patients (CPP)

Before starting biomedical research on human subjects, the sponsor has the obligation to submit the trial project to the opinion of one of the committees for the protection of patients which is competent in the area where the principal investigator is practicing.

A request for opinion on the biomedical research project is addressed to the committee by the sponsor.

Request of substantial modifications in the initial projects are submitted for the committee's opinion by the sponsor.

Favorable opinion has been released by the CPP Est III and AFSSAPS has authorized it.

11.2 Information and consent of the participants

Prior to carrying out biomedical research on human subjects, a free and written informed consent form must be signed by each individual participating in the trial after she/he has been informed by the investigator during a physician-patient consultation and after sufficient time for reflection has been allowed.

The information booklet and informed consent form (must be associated within the same document to insure that the whole information is given to the research participant.

The consent form must be dated and signed by both the participant in research and the investigator. All pages of the information booklet must be signed by the participant. The original document is archived by the investigator; a copy will be returned to the research participant.

In the case the objective of the trial is to carry out genomic or proteomic analysis, the information booklet must specify the type of research that will be undertaken and the patient must be given the right to accept or refuse that the biological samples taken from her/him be kept for the purpose of conducting scientific research.

11.3 Responsibilities of the sponsor

The sponsor of the trial, , is the moral person who: takes the initiative of conducting biomedical research on human subjects, and is therefore accountable for the research management and for verifying that the financing schedule covers the anticipated expenses.

The main sponsor responsibilities are:

- to subscribe a civil-responsibility insurance,
- to obtain an EudraCT (European Drug Regulatory Authorities Clinical Trials) identification number,
- to register the trial in the European data base,
- to request the opinion of the Committee for the Protection of Patients (CPP) on the initial project and the substantial amendments,
- to file the demand of authorization for the initial project and all substantial amendments with the competent authority,
- to provide information on the trial to the heads of the health care centers, the appropriate investigators and the pharmacists,
- to declare to the competent authorities, i.e. the ANSM and the EMEA (the European pharmacovigilance data bank, Eudravigilance) any suspicion of unexpected serious adverse events (U-SAE) related to any of the treatments used in the trial and communicate the information to the CPP and the investigators of the trial,
- to file annually the security report to the competent authority and the CPP,
- to declare the beginning and end of the trial to the competent authority,
- to edit the final report on the trial,
- to communicate the information on the trial's results to the competent authority, the CPP and the research participants,
- to archive the trial's essential documents in the sponsor folder for a minimal duration of 15 years after the research is ended.

11.4 Responsibilities of the clinical investigators

The main investigator of each health care center participating in the study commits to conducting the clinical trial in compliance with the study protocol that has been approved by the CPP and the competent authority (AFSSAPS/ANSM).

The investigator must not make any modification to the protocol without having obtained written authorization of the sponsor and the proposed modifications have been authorized by the CPP and the competent authority.

It is the responsibility of the main investigator:

- to provide the sponsor with its own curriculum vitae and co-investigators' curriculum vitas,
- to identify the members of its team who participate in the trial and to define their responsibilities,
- to start recruiting patients after the sponsor has issued its authorization.

It is the responsibility of each investigator:

- to collect the informed consent form, dated and signed personally by each individual research participant before any selection procedure specific to the trial may start,
- to regularly fill in the observation handbook (CRF) for each patient included in the trial and allow the clinical research assistant (CRA) mandated by the sponsor to have direct access to the source-documents in order to validate the data collected in the observation handbook.
- to date, correct and sign the corrections made in the observation handbook for each patient included in the trial,
- to accept regular visits of the study monitor and possibly the auditors as mandated by the sponsor or the inspectors of the competent legal authorities.

11.5 Collection of human biological sample(s)

Biological studies are necessary to advance the knowledge of diseases and could help in devising newer and more effective treatments. These studies are realized using human biological samples (blood, tumor tissues) that can be collected from patients either while they receive medical cares (examination, surgery) or specifically for the research purpose.

The revision of the law of bioethics in 2004 provides a legal framework for the use and storage of human biological samples, notably regarding the patient information and solicitation of his/her consent or the right of refusal according to the modalities by which the sample is collected. The law also foresees that after the biological studies has been completed and in the case the patient does not oppose it, the samples that were not completely used may be used in subsequent scientific research.

Additionally, it must be noted that the results of biological studies may be published under the condition that all the data relative to the patients are made anonymous.

As for research aimed at studying the genetic characteristics of the patients, a consent form must be signed by each participating patient after he has been informed on the research undertaken, irrespective of the type of sample collected (already existing or specifically collected).

11.5.1 Sample use and banking

During the medical cares of surgical interventions, that have been (or are going to be) realized, biological, tissues and/or cells samples (blood, tumor tissues) have been (or will be) collected for medical purposes. A part of these samples will be kept and use in scientific research.
The patient will be informed of this research and, if he/she agrees, the biological samples for the research study will be:

- (1) prepared and stored using a specific technic (freezing, fixation in paraffin or with nitrogen) to ensure its long-term preservation in excellent conditions.
- (2) used in this research (*see appendix 14*).

The preparation, storage and use of the biological samples does not modify or imply any change with respect to the diagnosis, cares, and treatments that will be administered to the patient.

The results from this research may be published later on in scientific journals; all data will be made anonymous.

Once the research is completed and if the patient does oppose it, the samples that have not been completely used may be used in further research.

11.6 Federation of the Patients Committee for Clinical Cancer Research (FCPRCC)

The creation of the Federation of the Patient Committees for Clinical Cancer Research (FPCCCR) was initiated by the UNICANCER (and the LNCC (National League for Treating Cancer). Its dedicated task is a second reading of the clinical trial protocols.

The patient committees' federation is coordinated by the BECT (Clinical and Therapeutic Trials Offices), a body of the UNICANCER.

It includes both the patient committees of the LNCC and from other health care centers.

It commits to: rereading the protocol and proposing improvements dealing principally with the quality of the letter of information to the patients, the setting up of a treatment and monitoring plan, and suggesting measures aimed at ameliorating the comfort of the patients.

12. RESEARCH DATA PROCESSING AND DOCUMENT ARCHIVING

12.1 Data processing and ownership

12.1.1 At the level of the sponsor

Statistical data analysis will be transferred to the Biostatistical Unit of the Institut Régional du Cancer de Montpellier / Val d'Aurelle under the responsibility of Sophie Gourgou-Bourgade. All data from the trial remain the property of UNICANCER, the research sponsor.

The software CaptureSystem will be used for data input, management and archiving.

Statistical analysis will be performed using the Stata v10.0. software.

In accordance with the revision of the law ‘’loi informatique et liberté’’ of August 6th, 2004 and its application decree, UNICANCER commits to complying with the reference MR001 methodology establish by the Commission Nationale de l’Informatique et des Libertés (French national commission on digital information and freedom).

12.1.2 In the investigational centers if digital medical records are used

In the case that digitized patient records are used in a participating center to process or store data related to the biomedical research, the center must:

a) verify and document that the computerized systems used to process the data is in conformity with the requirements in terms of data completeness, accuracy and reliability with respect to the expected performances (quality validation);
b) set up and follow up the standardized procedures related to these systems;
c) ensure that these systems allow modifications of the collected data, that each modification is automatically documented, and that no data can be removed (i.e., any change or modification of the data must be traceable);
d) set up and maintain a security control that prevents any unauthorized access to the data;
e) establish and regularly update the list of persons authorized to access and modify the data;
f) carry out appropriate backups of the data;
g) ensure confidentiality, whenever it is applicable (e.g. during data input);
h) ensure that the computerized patient personal data are processed within the framework of the research study according to the law on ‘’digital information and freedom’’ n° 78-17 of January 6, 1978 modified by the law n°2004-801 of August 6, 2004 and the texts regulating its application.

If data are transformed while being processed, it should always be possible to compare them with the original observations.

The computerized system used to identify the patients participating in the research must not be ambiguous and should allow the identification of all data collected for each patient while preserving their confidentiality in accordance with the law n° 78-17 modified.

12.2 Document archiving

All documents regarding the study (protocol, consent forms, observation handbook, investigator's files, etc.) as well the original documents (laboratory results, radiographies, patient records, clinical examination reports, etc.) must be kept in a locked and secured place and considered to be confidential material.

Data will be archived under the responsibility of the main investigator of each participating center according to the regulation in force (order of November 8, 2006). The archives will be kept as well as a list of patient identifications for a minimum period of 15 years after the end of the study.

13. DATA OWNERSHIP AND CONFIDENTIALITY MANAGEMENT

Until the trial results are published, the investigator is responsible for insuring the confidentiality of the totality of the information, handled by herself/himself and all other individuals involved in the course of the trial, supplied by UNICANCER .This obligation holds for the information that the investigator may communicate to the patients within the context of the trial and for any already published information as well.

The investigator commits not to publish, not to spread or use in any manner, directly or indirectly, the scientific and technical information related to the trial.

Nevertheless, in conformity with the article R 5121-13 of the Public Health Code, both the center and the investigator may communicate information relative to the trial:

- to the Health Minister,
- to the public health inspectors who are doctors,
- to the public health inspectors who are pharmacists,
- to the AFSSAPS General Director and inspectors.

The trial will not be the subject of any written note and/or oral comment without the prior agreement of the sponsor; the totality of the information that is communicated or obtained during the course of the trial belongs in full right to the Fédération Nationale de Lutte Contre le Cancer that can freely use it.

14. PUBLICATION RULES

Publishing PRODIGE trials within a reasonable time in peer-reviewed scientific journals with wide audience (good impact factors) is one essential objective for therapeutic progress. The Coordination Committee of PRODIGE (CCP) is responsible for ensuring that this objective is reached and will decide:

- when the preliminary and the final results of the study should be published.
- who are the members of the writing committee (maximum 5 members).

All information resulting from this trial is considered to be confidential, at least until appropriate analysis and checking has been completed by the sponsor, the principal investigator and the statistician of the trial.

The Coordination Committee may delegate its responsibilities to the principal investigator.

In any case, the CCP validates the choices that have been made by the writing committee regarding publishing and ensures that delays are respected. The absence of response from the CCP within a delay of one month implies acceptance.

1) The writing committee includes

- The principal investigator (and the associate principal investigator, if applicable) who has written the initial protocol. The principal investigator will be first author unless exceptionally decided otherwise.
- The statistician(s) who have performed the statistical data analysis;
- The most important contributors;
- Possibly, an expert who has contributed in an exceptional way to the data analysis (biologist, anatomopathologist,…).

2) The first author commits to produce a manuscript ready for publication within a delay determined by the CCP. The delay should not exceed one year after the end of the trial. In case the first author is in the unable to comply with this obligation another first author will be designated by the CPP. To help writing the articles related to the trials, the service of a medical writer may be used and working meetings organized in collaboration with the first author and the statistician(s).
Before any article is published, the list of patient inclusions per center and the list of clinical investigators participating in the trial will be made available to the all other investigators of the trial.

2) **Order of authors:** it will be determined according to their contribution and the number of patients included:

- The first author
- The members of the writing committee (as defined previously)
- A limited number of investigators, 1 per center, listed in decreasing order of importance (number of patients included). In some particular cases, the trial's steering committee may decide that 2 investigators from the same center are both authors. These criteria will be weighed to allow small centers with dedicated inclusion effort to be represented in the list of authors. The CCP will validate this process so that everyone's interests are preserved.
- The maximum number of authors authorized by the journal targeted for submission will be used.
- Irrespective of the number of included patients, there will be at least one author representing either the FFCD or UNICANCER.
- In articles reporting sub-studies, authors may differ from those of the principle article and reflects the scientific specialty involved; e.g.: in radiochemotherapy (RCT) trials an article dedicated to radiotherapy may be signed by radiotherapists who are participating as co-investigators. The first author of the princeps article will be last author in substudy publications (possibly referred to as "having equally contributed").
- The Prodige partnership must appear in the title or after the author list. In the case of cooperative trials, the first partnership quoted is the one that has initiated the trial. Other collaborative associations/partnerships are mentioned in order of their importance under the condition that they have included at least 5% of patients.
- With some exceptions, a member of the Inserm Unit 866 will be last author in trials sponsored or managed by FFCD, unless he/she is first author, to insure that the Inserm participation is represented. In that case, the author before the last author may be indicated as having "equally contributed" (if applicable).
- Usually the statistician appears after the third position in the author list. However, he/she may be first or second author in specific articles.

All the participants who do not appear in the author list are cited at the end of the article. The data manager is also cited or may appear in the author list if the CCP deems it justified.
Partners are acknowledged.
Before it is submitted to a journal, the authors and the sponsor will receive a copy of the manuscript. They commit to reading and sending it back with their written comments and criticisms within 15 working days (30 days during the summer semester).

4) Oral communications:

With a prior agreement from the CCP or the Steering Committee, an investigator may present orally on her/his behalf all or part of the results. The rules for citing authors are generally the same for oral presentations as for the published articles. However, the order of authors may differ between articles and oral communications and according to the congress wherein the research is presented. In some particular cases (e.g.: multidisciplinary, pathological, biological, echo-endoscopic studies conducted in parallel with the therapeutic trial) other authors may be selected. The PRODIGE partnership and other associations, if any, must be quoted as well.

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APPENDIX

- Appendix 1 : Resectability consensus
- Appendix 2 : Digestive oncology: surgical practices
- Appendix 3 : Recommendations for the surgery and anatomo-pathology teams
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- Appendix 7 : Declaration of Helsinki
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APPENDIX 1 : Consensus resectability criteria

Pancreatic cancer resectability criteria:

- No distant metastases,
- Clear fat planes around the celiac axis, hepatic artery, and superior mesenteric artery,
- No radiographic evidence of superior mesenteric vein and portal vein abutment, distortion, tumor thrombus, or venous encasement.
- no tumour invasion of the aorta,
- no partial (a few centimeters) or complete thrombosis of the portal vein or superior mesenteric vein,
- no circumferential encasement of the superior mesenteric artery, celiac axis or proximal hepatic artery.

In the absence of distant metastasis, the following tumor types will be classified as 'borderline resectable' (i.e., at the limit of resectability):

- Venous involvement of the superior mesenteric vein /portal vein demonstrating tumor abutment with or without impingement and narrowing of the lumen, encasement of the SMV/portal vein but without encasement of the nearby arteries, or short segment venous occlusion resulting from either tumor thrombus or encasement but with suitable vessel proximal and distal to the area of vessel involvement, allowing for safe resection and reconstruction.
- Gastroduodenal artery encasement up to the hepatic artery with either short segment encasement or direct abutment of the hepatic artery, without extension to the celiac axis
- Tumor abutment of the superior mesenteric artery not to exceed >180° of the circumference of the vessel wall

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APPENDIX 2 :
Digestive oncology : surgical practices

DIGESTIVE ONCOLOGY/ SURGICAL PRACTICES.
GUIDELINES OF THE FRENCH SOCIETY OF DIGESTIVE SURGERY AND THE FRENCH ASSOCIATION OF HEPATOBILIARY SURGERY AND LIVER TRANSPLANTATION

CANCER OF PANCREAS

✓ *CANCER OF THE HEAD OF PANCREAS (CEPHALIC TUMOR)*

- **Contraindications for pancreaticoduodenectomy** (Whipple resection)

Pancreaticoduodenectomy as surgical treatment of ductal adenocarcinoma must not be realized in case of:

- hepatic, peritoneal or distant lymph nodes (interaortico-caval involvement) metastases
- artery invasion (celiac axis, superior mesenteric artery, hepatic artery)
- complicated venous invasion (circumferential invasion, with cavernoma) or association with extension to the uncinate process with invasion of the arterial sheath.

- Staging

Preoperative staging of adenocarcinoma of the head of pancreas relies essentially on spiral computerized abdominal tomodensitometric (TDM) scan with arterial-parenchymal and portal vascular injection and fine cross-section (2 to 3 mm) centered in the upper abdomen supra-mesocolic area. In the presence of clearly resectable tumors (based on the result of this examination) the interest in systematically performing other explorative interventions (e.g. laparoscopy) is not demonstrated.
No evidence-based recommendation can be made towards the systematic dissection of the aortico-cave lymph nodes or even just the grossly involved ones ('berry picking' procedure). At this level, the determination of a macroscopically suspect lymph node implies its extemporaneous examination; if it is a metastatic lymph node, pancreatectomy is contraindicated.

- **The pancreaticoduodenectomy technique**

Except in cases of suspected invasion of the uncinate process a circumstance wherein the superior mesenteric artery (SMA) is to be controlled first, before a digestive or pancreatic resection (expert consensus), R0 resection of cephalic adenocarcinoma must include the following steps (Grade C):

- dissection of main bile duct under the superior biliary confluence; skeletonization of the hepatic artery and pedicular portal vein,
- pancreatic isthmus dissection with systematic histological extemporaneous examination of the resection cross section,
- dissection and circumferential mobilization of the mesenteric-portal vein axis,
- exposition of the SMA right hemi-circumference, allowing complete excision of the uncinate process During pancreaticoduodenectomy performed for head pancreatic adenocarcinoma, regional lymphadenectomy is recommended and must remove peri-pancreatic lymph nodes: anterior and posterior lymph nodes, hepatic common and along the proper hepatic artery lymph nodes, hepatic pedicle lymph nodes, and lymph nodes located on the right border of the celiac axis and SMA (Grade C).

Extended lymphadenectomy which removes all celiac relays on the left border of SMA and the aortico-cave lymph nodes is not recommended.
It is recommended, according to the surgeon's usual practice, to perform either pancreaticoduodenectomy with pyloric preservation or pancreaticoduodenectomy with distal gastrectomy, because these two techniques have equivalent comorbidities and identical distant prognosis (Grade A). However, pancreaticoduodenectomy with antrectomy is recommended if the tumor location (upper part of the head) exposes the patient to a risk of R1 resection in the case of pyloric preservation.
It is recommended to broaden en bloc pancreaticoduodenectomy (Grade C):

- to the mesenteric-portal vein axis, when neoplastic invasion is limited to the venous axis, because it may allow curative resection (R0), with rates of: a) postoperative mortality and morbidity and b) survival that are comparable with those obtained with pancreaticoduodenectomy without necessary venous dissection,
- to the right colon, in the case of mesocolon invasion.

It is recommended that a preliminary evaluation of the operative specimen is made by the surgeon with indications of the resection margins and possible vascular involvement (Grade C).

✓ *SURGERY FOR LEFT-SIDED PANCREATIC CANCER*

Caudal pancreatectomy for duct adenocarcinoma is contraindicated in case of hepatic, peritoneal, or distant lymph nodes (interaortico-caval) metastatic involvement, arterial invasion(superior mesenteric artery, hepatic artery) (Grade C).
In the cases of venous invasion at the splenomesaraic confluence or arterial invasion at the level of the celiac axis, the possibility of resection may be discussed for patients presenting a low risk of surgical complications, and under the condition that the vascular resection allows R0 resection.
Laparoscopy is recommended to search for hepatic and/or peritoneal metastases in left-sided pancreatic adenocarcinoma (Grade C).
R0 resection of left-sided adenocarcinoma must include the following steps:

- isthmus resection in proximity of the gastroduodenal artery,
- skeletonization of the hepatic artery and mesenteric-portal vein axis,
- tying of the proximal splenic vessels,
- dissection of the left side of the celiac axis and SMA,
- en block mobilization of the tumor via opening of the posterior mesogastrium, or in case of suspected tumoral invasion of the left pararenal fascia, opening of the pararenal space.

Preparation of the operative specimen must follow the same rules as for pancreaticoduodenectomy (see previous section).

APPENDIX 3 :
Recommendations for the surgery and anatomo-pathological teams

For the surgical teams :

- Orient the tumor specimen so that the resection limits can be clearly identified, in particular indicate the pancreatic cross section with strings.
- It is recommended that the surgeon prepares the tumor specimen by inking the resection margins and indicates a possible vascular invasion.
- The pancreatic posterior margin and especially the margin of the **higher mesenteric artery** ("retroperitoneal" or **medial margin**) must be inked, with inks of two different colors ideally by the surgeon himself. In this case, it is necessary to take care of well drying the ink or to fix it (acid acetic) to avoid spreading ink on all the parts.
- Locoregional lymphadenectomy is recommended, including the removal of the anterior and posterior peri-pancreatic lymph nodes, hepatic lymph nodes (common and along the proper hepatic artery), hepatic pedicle lymph nodes and those situated on the right border of the celiac axis and superior mesenteric artery.
- An extemporaneous histological examination of the isthmian pancreatic slice section is recommended in the event of DPC.

For the anatomo-pathological teams:

- The margin on the higher mesenteric artery must be inked during the macroscopic evaluation of the part if the surgeon did not already do it.
- The conjunctive tissue between the anterior surface of the lower vena cava and the posterior face of the head of the pancreas and the duodenum must be called pancreatic posterior margin (and not retroperitoneal margin).
- According to the TNM classification, it is desirable to obtain at least 10 ganglia to determine the stage of the disease. In more recent studies, it is at least 12 to 15 ganglia it would be necessary to have.
- In this protocol, R1 is defined like a margin ≤ 1 mm (www.rcpath.org), with the exception of the anterior surface of the pancreas, which cannot be regarded as a true margin.

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In : Cancer du pancréas, rapport présenté au 112e Congrès français de chirurgie, Paris, 6-8 octobre 2010
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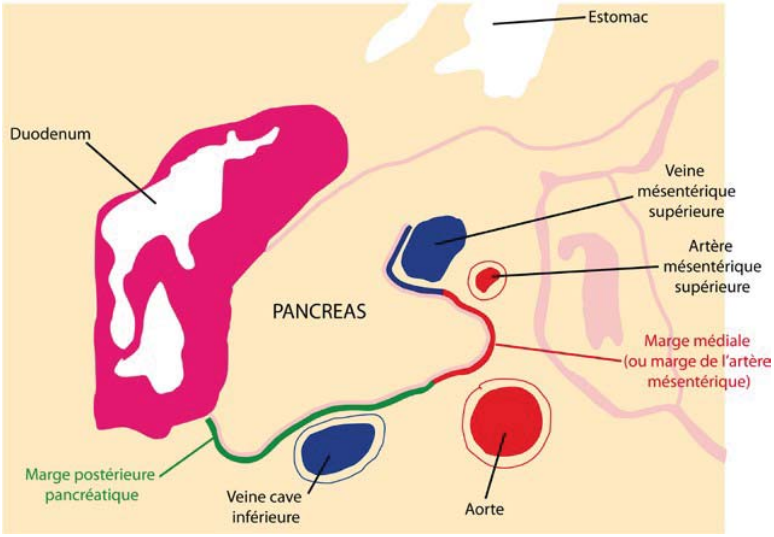

Courtesy F Gillet and JR Delpero

APPENDIX 4 :
Adenocarcinoma of the exocrine pancreas and ductal adenocarcinoma: definition

Classical and rare forms of ductal adenocarcinomas are eligible:

Histological variants of ductal carcinomas that may be included in the protocol:

- mucinous non-cystic adenocarcinoma,
- signet ring cell carcinoma,
- adenosquamous carcinoma,
- undifferentiated or anaplastic carcinoma,
- mixed ductal-endocrine carcinoma,
- undifferentiated carcinoma with osteoclast-like giant cells,

In peri-ampullary adenocarcinomas, adenocarcinomas developed in the duodenal mucosa or in the ampulla epithelium, or in the bottom half of the bile duct are not eligible, whereas adenocarcinomas developing from the head of pancreas are eligible.

Classification WHO 2010. Ductal adenocarcinoma of the pancreas. Klöppel G et al. pages 221-230

http://www.iarc.fr/en/publications/pdfs-online/pat-gen/bb2/bb2-chap10.pdf,

Histological grade: it is determined according to the glandular differentiation, mucus production, mitotic index and nuclear atypia.

Grade 1: **well differentiated**, tumor cells with regular cylindrical shape, low polymorphism, nuclei in the basal position, abundant mucus secretions, and at most 5 mitoses/10 HPF

Grade 2: **moderately differentiated**, duct-like structures and tubular glands, moderate polymorphism, 6 to 10 mitoses/10 HPF, low mucus-secretion.

Grade 3: **poorly differentiated**, sizeable nuclear polymorphism, enlarged nuclei, more than 10 mitoses/10 HPF, low mucus production, marked atypia.

.

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Carcinoma of the exocrine pancreas: the histology report.
Dig Liver Dis. 2011;43 Suppl 4:S282-92.

APPENDIX 5 :
Histopathological classification pTNM 2009 for the pancreas

Anatomical subtypes

1. Head of pancreas

- Tumors of the head of pancreas are those arising to the right of the left border of the superior mesenteric vein. The uncinate process is considered as part of the head.

2. Body of pancreas

- Tumors of the body are those arising between the left border of the superior mesenteric vein and the left border of the aorta.

3. Tail of pancreas

- Tumors of the tail are those arising between the left border of the aorta and the hilum of spleen.

Regional lymph nodes

- The regional lymph nodes are the peripancreatic nodes, which may be subdivided as follows:

superior	superior to head and body
inferior	Inferior to head and body
anterior	anterior pancreaticoduodenal, pyloric (for tumors of head only) and proximal mesenteric
posterior	posterior pancreaticoduodenal, common bile duct, and proximal mesenteric
splenic	hilum of spleen and tail of pancreas (for tumors of head)
coeliac	(for tumors of head only)

TNM Clinical classification 2009, 7th edition

T- Primary tumor

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ**
T1	Tumor limited to pancreas, 2 cm or less in greatest dimension
T2	Tumor limited to pancreas, > 2 cm in greatest dimension
T3	Tumor extends beyond pancreas, but without involvement of coeliac axis or superior mesenteric artery
T4	Tumor involves coeliac axis or superior mesenteric artery (non resectable tumor).

*Tis also includes the 'PanIN-III' classification

N- Regional lymph nodes

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis.

M- Distant Metastasis

MX	Distant-metastases cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

- Classify the disease as M1 when there is the presence of peritoneal carcinomatosis, tumor cells in ascites. In the absence of ascites, a positive peritoneal washing is also considered M1 (AJCC Cancer Staging Manual, 7th ed.).

Histopathological pTNM classification

- The pT, pN and pM categories correspond to T, N and M categories

pN0

Histological examination of the regional lymphadenectomy specimen will ordinarily include 10 or more lymph nodes. If the lymph nodes are negative but the number ordinarily examined is not met, classify as pN0.

In the case of primary tumor surgery, the resection quality must be assessed;

Rx: presence of residual tumor cannot be assessed

R0: No residual tumor, complete macroscopic and microscopic resection (negative margin)

R1: positive resection margin (microscopic residues)

R2: macroscopic tumor residues

Quality of the resection specimen is not part of the TNM classification, but it is an important prognosis factor (AJCC Cancer Staging Manual, 7th ed.).

Stage grouping

Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1, T2, T3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

APPENDIX 6 :
Performance status evaluation – WHO scale

Performance status ECOG-ZUBROD/ WHO	value
Fully active, able to carry on all pre-disease performance without Restriction.	0
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.	1
Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours	2
Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	3
Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	4

APPENDIX 7 :
World Medical Association
Declaration of Helsinki

WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington, DC, USA, October 2002
(Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo, Japan, October 2004
(Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, Korea, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects**,** including research on identifiable human material and data.
The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.
2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.
3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."
5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.
6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.
7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
8. In medical practice and in medical research, most interventions involve risks and burdens.
9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.
10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.
14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.
15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.
16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.
17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.
18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.
19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.
20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.
21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.
22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.
23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.
24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.
25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In

such situations the research may be done only after consideration and approval of a research ethics committee.
26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.
27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.
28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.
29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.
30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE
31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:

- The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
- Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.
34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.
35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

APPENDIX 8 :
Modalities for the investigational products preparation and administration

1 – IRINOTECAN (CAMPTO®)

Irinotecan, a semi-synthetic derivative of camptothecin, is an antineoplastic agent which acts as a specific inhibitor of DNA topoisomerase I. In most tissues, irinotecan is metabolized into SN-38 by carboxylesterase. Tested against several murine and human tumor cell lines, SN-38 was found to be more active than irinotecan in purified topoisomerase I and more cytotoxic than irinotecan. The inhibition of DNA topoisomerase I by irinotecan or SN-38 induces single-strand DNA lesions which blocks the DNA replication fork and are responsible for the cytotoxic activity of irinotecan which is time dependent and specific to the S phase.

Pharmaceutical form
Concentrate for solution for injection, supplied in vials containing either 40 mg or 100 mg in 2 ml or 5 ml, respectively, with a concentration of 20 mg/ml.

Preparation

Aseptically withdraw the required amount of Irinotecan concentrate from the vial with a calibrated syringe and inject it into a 250 ml infusion bag or bottle containing either 0.9 % sodium chloride solution or 5% dextrose solution. The infusion should then be thoroughly mixed by manual rotation.

Shelf life and storage

Vials must be kept in the outer carton in order to protect from light.
The Irinotecan concentrate for solution for infusion should be diluted and used immediately after opening. However, if dilution takes place in controlled and validated aseptic conditions, the Campto® solution for infusion can be used (infusion time included) within 12 hours when stored at room temperature, or within 24 hours when stored in a refrigerator at 2 to 8°C after dilution/reconstitution.

2 – OXALIPLATIN (ELOXATIN®)

Oxaliplatin is an antineoplastic agent belonging to a new class of platinum-based compounds in which the platinum atom is complexed with 1,2-diaminocyclohexane ("DACH") and an oxalate group. Oxaliplatin is a single enantiomer, (*SP*-4-2)-[(1*R*,2*R*)-Cyclohexane-1,2-diamine-k*N*,k*N'*] [ethanedioato(2-)-k*O1*, k*O2*] platinum (cis-[oxalato (trans 1-1-1,2-DACH) platinum). Oxaliplatin exhibits a wide spectrum of both *in vitro* cytotoxicity and *in vivo* antitumour activity in a variety of tumor model systems, including human colorectal cancer models. Oxaliplatin also demonstrates *in vitro* and *in vivo* activity in various cisplatin-resistant models. A synergistic cytotoxic action has been observed in combination with 5-fluorouracil both *in vitro* and *in vivo*. Studies on the mechanism of action, although not completely elucidated, show that the aqua-derivatives resulting from the biotransformation of oxaliplatin interact with DNA to form both intra and inter-strand crosslinks, resulting in the disruption of DNA synthesis, leading to cytotoxic and antitumor effects.

Pharmaceutical form
Concentrate for solution for infusion, dosage at 50 mg and 100 mg,

Preparation
Dilute the vial in ppi water or in glucose solution at 5%, containing 5 mg of oxaliplatin per ml.
To obtain an oxaliplatin solution diluted at 5 mg/ml, add 10 ml of solvent to the 50 mg concentrate, or 20 ml solvent to 100 mg concentrate.

Shelf life
After dilution in 5% glucose, chemical and physical in-use stability has been demonstrated for 48 hours at +2°C to +8°C and for 24 hours at +25°C. From a microbiological point of view, this infusion preparation should be used immediately. If not used immediately, in-use storage times and conditions prior to use are

the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C unless dilution has taken place in controlled and validated aseptic conditions.

3 – 5-FLUOROURACIL

Fluorouracil is a cytostatic antineoplastic agent from the class of antimetabolites (antipyrimidine). The fluorouracil antitumor activity is related to the fact that it is an analog of uracil, a component of ribonucleic acid, that plays a fundamental role in the fast growing tissues in several ways: as a precursor (via the thymidilate synthetase) of thymine, a nucleotide necessary to the DNA synthesis and cell replication; it also enters in the composition of RNAs that controls the synthesis of proteins and enzymes.

Pharmaceutical form

Concentrate for solution for infusion is available in vials containing respectively 250 mg, 500 mg, 1g and 5 g, in 5 ml, 10ml, 20 ml and 100 ml, to be diluted to 50 mg/ml.

Route of administration

Intravenous infusion. Do not inject intramuscularly. In case of extravasation, infusion should be stopped immediately.

Dilution: 15 ml of concentrate can be diluted in 250 ml using the following solutions:

- sodium chloride 0.9%
- glucose 5%
- glucose 10%
- glucose 2.5% + sodium chloride 0.45%
- Ringer's solution
- Hartmann's solution

Shelf life

Do not store above 25°C. Keep container in the outer carton to protect from light. Do not refrigerate.

Store the preparation at a temperature between + 15°C and +25°C. After dilution, immediate use is recommended. However, chemical and physical in-use stability has been demonstrated for 8 hours at a temperature between + 15°C and +25°C.

4 - L-FOLINIC ACID

Folinic acid is a metabolically active form of folic acid. It is an antianemic agent (belonging to the vitamin B group: involved in blood and hematopoietic organs). It is a biochemical antagonist of antifolic agents such as methotrexate (specifically), pyrimethamine, and to a lesser extent salazopyrine. The levogyre folinic acid (L-folinic acid) is the active form of DL-folinic acid (racemic mixture). A dose of the L isomere corresponds to half a dose of the racemic mixture (DL). The efficacy and undesirable effects of the L isomere are identical to those of the racemic mixture.

Pharmaceutical form

The product is available in vials of lyophilisate powder 25 mg for solution for parenteral use, and in solution for injection IM or IV at 25 mg/2.5 ml concentration.

Shelf life

The lyophilisat must be kept at a temperature < 30 °C, protected from light and humidity. After preparation, the solution may be kept for 24 hours below 30 °C. It may be conserved longer in a refrigerator at a temperature between 2°C and 8°C and in the dark.

5 – GEMCITABINE (GEMZAR®)

Pharmaceutical form

Gemcitabine is available in lyophilized powder for solution for injection in sterile glass vials containing 200 mg or 1 g of gemcitabine hydrochloride (expressed as free base), mannitol and sodium acetate.

Preparation

The recommended solvent for the reconstituted solution of Gemzar® is a sodium chloride solution at 0.9%. Vials will be diluted by adding isotonic salt serum to a solution containing ideally 10 mg/ml at most. The concentration for vials of 200mg and 1g should not exceed 40 mg/ml.

Route of administration

Continuous IV infusion over 30 minutes.

Shelf life

The lyophilized product must be kept below 3°C. As soon as the solution is reconstituted, it should be kept at room temperature and used within 24 hours. Do not store the reconstituted solution in a refrigerator.

APPENDIX 9 :
Recommendations for the use of Granocyte®

Name of the product

GRANOCYTE 34 (33.6 x 106 IU/1 ml), freeze-dried powder in vial and solvent in prefilled syringe for injectable solution (SC or IV infusion).

Qualitative and quantitative composition

Lenograstim* (rHuG-CSF) 33.6 x 106 IU (equivalent to 263 micrograms) per ml after reconstitution.

*Recombinant glycoprotein (rHuG-CSF) equivalent to the Human Granocyte Colony Stimulating Factor isolated from CHU-2, a human cell line. Lenograstim is expressed and glycosylated in a mammalian host cell system : chinese hamster ovary (CHO) cells.

Excipient with notorious effects: phenylalanine.

Pharmaceutical form

Lyophilisate and solvent for injectable solution (white powder, solvent: clear and colorless solution)

Therapeutic indications

Reduction in duration of neutropenia and associated complications in patients undergoing bone marrow transplantation or cytotoxic chemotherapy associated with a febrile neutropenia.

Posology and route of administration

Treatment must be administered only in cooperation with an establishment experienced in oncology and/or hematology.

Granocyte may be administered either by subcutaneous injection or intravenous infusion.

The recommended dose of GRANOCYTE is 150 µg (19.2 MUI) per m² and per day, equivalent dose in efficacy to 5 µg (0.64 MIU) per Kg and per day.

Granocyte 34 millions UI/ml is used in patients with a body surface area up to 1.8 m².

In adults

After established cytotoxic chemotherapy, Granocyte should be administered daily at the recommended dose of 150 µg (19.2 MUI) per m² and per day as a subcutaneous injection. The first dose should not be administered less than 24 hours after the cytotoxic chemotherapy. Daily administration of Granocyte should be continued until the expected nadir has passed and the neutrophil count returns to a stable level compatible with treatment discontinuation, with, if necessary, a maximum of 28 consecutive days of treatment. Even if a transient increase in neutrophil count occurs during the first two days of treatment with the continuation of treatment, the nadir usually occurs earlier and recovery is quicker.

Contraindications

GRANOCYTE should not be administered to patients with known hypersensitivity to the product or its constituents.

Granocyte should not be used to increase the dose intensity of cytotoxic chemotherapy beyond established dosage regimens and time courses since the drug could reduce myelotoxicity but not overall toxicity of cytotoxic drugs.

Granocyte should not be administered concurrently with cytotoxic chemotherapy.

Granocyte should not be administered to patients suffering from myeloid neoplasia other than *de novo* acute myeloid leukemia, with age < 55 years and/or good cytogenetic indicator, e.g. t(8;21), t(15;17) and inv(16).

Undesirable effects

In case of peripheral blood stem cell graft or bone marrow transplantation and chemotherapy-induced neutropenia

In controlled trials, the incidence of adverse events most frequently reported (15%) was identical in patients treated with Granocyte or placebo. Adverse events were those generally observed in conditioning protocols and were apparently not attributable to GRANOCYTE. These events consisted of: infection/inflammatory disorder of the buccal cavity, stomatitis, and fever, diarrhea skin rash, vomiting alopecia, septic episode and headache.

Based on data from clinical and postmarketing experience, frequencies of adverse events shown in the table are listed as follow: very common (≥ 10%); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to ≤ 1/100); rare (≥ 1/10000 to ≤ 1/1000); very rare (≤ 1/10000); not known (cannot be estimated from the available data).

Organ system Classes (MedDRA)	Very common	Common	Uncommon	Rare	Very rare
Investigations	LDH increase				
Blood and lymphatic disorders	Hyperleukocytosis, Thrombocytopenia	Splenomegaly			Splenic rupture (5)
Nervous system disorders	Headache Asthenia				
Respiratory, thoracic and mediastinal disorders				Pulmonary edema (3), Interstitial Pneumonitis, Pulmonary infiltrate, Pulmonary fibrosis	
Gastrointestinal disorders		Abdominal pain			
Skin and subcutaneous tissue disorders					Cutaneous vasculitis, Sweet's syndrome (4), erythematous nodules, Pyoderma gangrenosum, Lyell's syndrome
Musculoskeletal and connective tissue disorders	Skeletal pain, Dorsal pain	Pain (1)			
General disorder		Localized			

and administration site conditions		reactions near the site of injection			
Immune system disorders					Allergic reaction, Anaphylactic shock
Hepatobiliary disorders	Increase of ASAT/ALAT (2), Increase of alkaline phosphatases				

1 / The risk of pain increase in patients with elevated leucocyte count, especially when leucocytes ≥ 50 x 10^9/l.

2 / Transient increase of ASAT and/or ALAT was observed. In most cases, the hepatic function abnormalities were reversed after treatment with lenograstim was stopped.

3 / Some cases of impaired respiratory function or acute respiratory distress syndrome (ARDS) with potential fatal implications have been reported.

4 / Cases of Sweet's syndrome, erythema nodosum and pyoderma gangrenosum have been reported principally in patients presenting malignant hemopathies, a condition known to be associated with a neutrophil dermatosis, but also in patients with non-malignant neutropenia.

5 / Splenic rupture after administration de G-CSF administration was reported in healthy donators and in patients.

APPENDIX 10 :
Recommendations for patients treated with mFolfirinox

Dear patient,

You are about to receive FOLFIRINOX chemotherapy, that is to say an association of 3 anticancer drugs (5-Fluorouracil, Oxaliplatin and Campto®) and a vitamin (folinic acid). This treatment is usually well tolerated. However, the risk of side effects exists. Obviously, you will not be affected by each of the undesirable effects listed below, and if some of them occur their intensity may be very moderate.

Most side effects are related to Campto® (Irinotecan or CPT11).

– **during infusion or immediately after:**

Nausea, vomiting, diarrhea, abdominal cramping, vertigo, dizziness, vision disorder (e.g. impression of seeing double), lacrimation, and excessive saliva or sweating may occur. If one of these symptoms appears, call the nurse of the service section where you are treated. These symptoms will disappear rapidly, spontaneously or after a subcutaneous injection of atropine, if you do not have any contraindication to this product (glaucoma, prostate problem).

– **within a few days after infusion :**

Diarrhea may occur, in some cases, around the 5th day after infusion. If not treated rapidly with appropriate medication it may become very serious. All medications against constipation (laxative medication) must of course be stopped and any aliment/nutrient that may accelerate the intestinal transit should be avoided (e.g. milk products, raw vegetables, calorie supplements, spicy food, fruit juice, alcohol). We advise you to drink at least 8 to 10 glasses of water every day (1.5 liter), possibly with salt (sparkling water, sodas, soups). It is preferable to eat frequently and take small meals: rice, pastas, bananas, stewed apples, toasts.

In case of diarrhea or abdominal cramping, contact the physician who has prescribed irinotecan to you. As soon as the first liquid stool appears, take two capsules (4 mg) of loperamide (medication existing under several brand names: Imodium® or Altocel®, Imossel®, Nabutil®, Nimaz®, Dyspagon®, Ercestop®, loperamide (generic)), treatment to be continued with two capsules of 2 mg to be taken every 2 hours (2 capsules every 4 hours at night), for at least 12 hours. In any case, continue treatment with loperamide for 12 hours after the last liquid stool.

Please, do not decide on your own to modify the dose or treatment duration.

If, despite the anti-diarrheic treatment (loperamide), diarrhea persists more than 48 hours, you must contact your physician or oncologist, and start the antibiotic treatment that was prescribed for you, usually Oflocet®, 1 tablet on mornings and evenings (2 tablets of 200 mg per day) for 7 days. Your treatment with loperamide will be stopped, it should not last more than 48 hours in total.

If diarrhea is not stopped within 96 hours, that is to say, 4 days after the treatment against diarrhea has started (2 days of loperamide only plus 2 days of Oflocet® according to the table below) you must imperatively contact your physician who will take the decision to hospitalize you for a few days. A blood test (platelets count, potassium, creatinine level) is often useful.

First Liquid stool ↓ — If persistent diarrhea:

			Oflocet	Oflocet	Oflocet	Oflocet	Oflocet	Oflocet	Oflocet
	Loperamide	Loperamide							
Day :	D1	D2	D3	D4	D5	D6	D7	D8	D9

↓

Hospitalization is necessary if persistent diarrhea

If you nausea and vomiting prevent you from drinking or taking your treatment against diarrhea, or if diarrhea is associated with fever, or if you feel intense fatigue at the same time as diarrhea, contact your physician straight away.

Never take the anti-diarrheic treatment preventively (no loperamide without diarrhea), but only in case of soft or liquid stool.

Fever may be the sign of a serious infection if, at the same time, your white cell count is lowered. In this case, contact rapidly your physician who will take the appropriate decision.

The risk of nausea and vomiting is usually well controlled by the medications you will receive before treatment with oxaliplatin. At home, please, take the treatment prescribed for you. If this is insufficient, do not hesitate to call your physician. Avoid fried food, fat foods or those with a strong smell. If the food smells provoke nausea, eat cold or slowly warmed food.

With chemotherapy, the taste of food may change (taste of papier-mâché, iron filings). There is no specific treatment for this inconvenience; however, mint candies may help.

Chemotherapy may cause fatigue, with a temporary and moderate decrease of visual acuity, in particular on evenings. It is therefore not advised to order new glasses during the chemotherapy period. Eyes fatigue will disappear at the end of treatment.

Irinotecan may induce hair loss. You may sometimes be offered the use of a refrigerating helmet during chemotherapy to avoid hair loss. If hair loss occurs anyway, talk with your oncologist who will prescribe a capillary prosthesis.

Efficient contraception must be maintained all over the chemotherapy duration.

Other undesirable effects related to oxaliplatin:

Oxaliplatin may be responsible for sensations of swarming (ants crawling) or tingling on your hands and feet. In cold weather, these sensations may also occur around your mouth, near the nostrils, at the extremity of ears. Sometimes, swarming may occur inside the mouth bouche and cause pains. In that case, you need to avoid cold drinks or ice cream. Aliments must be taken out of the refrigerator one hour in advance and warmed. While eating, you may have jaw cramps from the first bite. Inform your physician of the occurrence of all these side effects and their durations, especially if you have difficulty to write or fasten a button to your clothes. Occasionally, oxaliplatin may be responsible for allergic manifestations.

What to do in case of swarming?

- Avoid exposure to cold: do not stay outside when it is cold, avoid the fresh fruit section of the supermarkets, as well as sections with refrigerators or freezers.
- Protect your hands with glows.
- Do not wash your hands with cold water.
- Do not eat cold food.
- Do not drink cold.
- If swarms become a problem, wash your hands with warm water.

Other undesirable effects related to 5 Fluorouracil^{V} (5-FU):

- 5-FU may cause irritation of the mouth, in particular sores on the gums. However, the risk of sores is limited by a good dental hygiene. This is why we advise you to have dental descaling and the removal of possible tooth root infections.
- 5-FU favors sunburns. In case of sun exposure, we advise to use a total sun protection cream (index >25).
- Other rare undesirable effects are: redness of the palms of hands and soles of feet, conjunctivitis or stains of blood while blowing your nose.

– Interactions with other drugs or medications:

Please, inform us about any other medication or treatment you may receive. The drugs used in this protocol of chemotherapy have potential interactions with phenytoin (Dihydan®, Dilantin®), warfarin (Coumadin®), metronidazole (Flagyl®), allopurinol (Zyloric®), and Becilan®.
Influenza vaccine is authorized. Live or attenuated vaccines (prepared from living organisms) (drinkable polio vaccine, BCG, measles, mumps, rubella, yellow fever…) are forbidden.

Please, consult your oncologist if you need any additional information. In case of emergency, consult your physician without delay.

APPENDIX 11 :
Information for patients treated with Gemcitabine (GEMZAR®)

Dear Patient,

You are about to be treated with Gemcitabine, a chemotherapy that is usually well tolerated. It will be administered by intravenous infusion every week, for 3 weeks followed by one week of rest. A blood test will be realized the day before each injection.

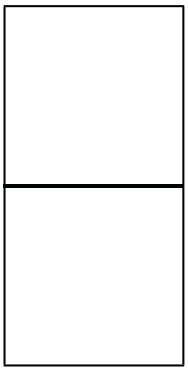
All undesirable side effects that may occur are listed below. Obviously, you will not be affected by each of the following side effects, and their intensity may be very moderate if they occur.

- Low risk of hair loss. Hair always grow again, 4 to 8 weeks after the last chemotherapy course.
- Nausea: rare, they may be attenuated by the prescription of medication against nausea before the chemotherapy infusion.
- You may have fever and muscular pain during the night following infusion. They may be attenuated by the intake of 1 gr of Tylenol (e.g. Doliprane®, Efferalgan®, Dafalgan® or generic tylenol).
- More rarely, you may have diarrhea or mouth sores.
- Sometimes, allergic manifestations with rashes may occur.
- Possibility of edema on the legs.
- Chemotherapy generally induces a decrease of blood white cells. Normally, this is without consequence, but a high fever (temperature > 38°C for more than 3 hours or higher than 38.5°C) may be the sign of a serious infection. In that case, you must call your physician who will prescribe a blood test: blood count with platelets, the result of which is to be awaited urgently.
- An elevation of liver enzymes (transaminases) may shows up in the blood tests. This is without consequence for you, but the dose of Gemcitabine will be decreased.
- If you are breathless following gemcitabine infusion, you need to inform your physician. Breathlessness is usually of short duration and disappears with no particular treatment.
- Influenza vaccine is authorized. Live vaccines (drinkable polio vaccine, BCG, yellow fever…) are forbidden.
- Efficient contraception is mandatory for the overall treatment duration.
- In rare cases, you may develop a progressive intolerance to gemcitabine, manifested by a fever increasingly elevating after each injection, fatigue, edemas of the legs, breathlessness and transaminase elevation. The intensity of all these reactions may increase with the number of injections. This type of reaction is fortunately uncommon.

Please, do not hesitate to inform your physician of the side effects and symptoms you have experienced, and in case of emergency, consult your family doctor.

APPENDIX 12 :
NCI- CTCAE Version 4.0 criteria

Please, refer to the CTCAE toxicity evaluation scale provided separately in attached documents or download it from the NCI website.



http://ctep.cancer.gov/

Common Terminology Criteria for Adverse Events v4.0 (CTCAE) (Publish Date October 1, 2009)

APPENDIX 13 :
List of expected SAEs

Extracts from the SPC for oxaliplatin - ELOXATIN®

DC/UNDESIRABLE SIDE EFFECTS

The frequencies reported in the table below are derived from clinical trials of oxaliplatin in the treatment of colorectal metastatic cancer, including 244 patient treated with oxaliplatin monotherapy and about 1500 patients with the oxaliplatin + 5-FU/FA combination.

- **Hematopoietic system disorders:**

Oxaliplatin administered as monotherapy (130 mg/m^2 every 3 weeks) causes a few grade 3 and 4 hematological toxicities.

Oxaliplatin monotherapy	Any grade	Grade 3	Grade 4
Anemia (% patients)	64	3	< 1
Neutropenia (% patients)	15	2	< 1
Thrombocytopenia (% patients)	41	2	< 1

When oxaliplatin is used in combination with 5-fluorouracil and folinic acid, the frequency of neutropenias and thrombocytopenia is higher compared with the association 5-fluorouracil/folinic acid.

Oxaliplatin combined with 5-fluorouracil	85 mg/m^2 every 2 weeks		
	Any grade	Grade 3	Grade 4
Anemia (% patients)	83	4	< 1
Neutropenia (% patients)	66	25	13
Thrombocytopenia (% patients)	76	3	< 1

- Digestive disorders:

As monotherapy, oxaliplatin (130 mg/m^2 every 3 weeks) may cause anorexia, nausea and vomiting, diarrhea and abdominal pains, which are moderate in the majority of cases.

Oxaliplatin monotherapy	Any grade	Grade 3	Grade 4
Nausea and vomiting (% patients)	69	12	2
Diarrhea (% patients)	41	4	< 1
Mucositis (% patients)	4	< 1	< 1
Hepatic abnormalities (% patients)	46	10	2

Prophylaxis and/or treatment with potent anti-emetic agents are indicated. When oxaliplatin is associated with 5-fluorouracil (with or without folinic acid) the frequency and severity of diarrheas and mucositis aresignificantly increased compared with 5-fluorouracil alone.

Rare cases of colitis, including *Clostridium difficile* diarrheas have been reported. Dehydration, paralytic ileus, intestinal obstruction, hypokalemia, metabolic acidosis and renal impairment may be caused by severe diarrhea/emesis particularly when combining oxaliplatin with 5-fluorouracil (5FU).

Oxaliplatin combined with 5-fluorouracil	85 mg/m ^{2} every 2 weeks		
	Any grade	Grade 3	Grade 4
Nausea and vomiting (% patients)	71	11	1
Diarrhea (% patients)	58	7	3
Mucositis (% patients)	42	7	1

Hepatic enzymes elevations of grade 1 and 2 are common during treatment with oxaliplatin. In randomized studies comparing the 5-fluorouracil/folinic association with the 5-fluorouracile/folinic acid/oxaliplatin association, the frequency of hepatic enzymes elevation of grade 3 and 4 is comparable in the two groups.

- **Nervous system disorders:**

The dose limiting toxicity of oxaliplatin is neurological. It involves a sensory peripheral neuropathy characterized by dysaesthesia and/or paraesthesia of the extremities with or without cramps, often triggered by the cold. These symptoms occur in up to 95% of patients treated. The duration of these symptoms, which usually regress between courses of treatment, increases with the number of treatment cycles.
The onset of pain and/or a functional disorder are indications, depending on the duration of the symptoms, for dose adjustment, or even treatment discontinuation.
This functional disorder includes difficulties in executing delicate movements and is a possible consequence of sensory impairment. The risk of occurrence of persistent symptoms for a cumulative dose of 800 mg/m² (10 cycles) is approximaly15% or less. The symptoms improve usually or totally recover after treatment discontinuation.

Acute neurosensory manifestations have been reported. They start within hours of administration and often occur on exposure to cold. They usually present as transient paresthesia, dysesthesia and hypoesthesia, or even as acute syndrome of pharyngolaryngeal dysesthesia. An acute syndrome of pharyngolaryngeal dysesthesia occurs in 1% - 2% of patients and is characterized by subjective sensations of dysphagia or dyspnea feeling of suffocation, without any objective evidence of respiratory distress (no cyanosis or hypoxia) or of laryngospasm or bronchospasm (no stridor or wheezing); occasionally other symptoms that have been observed include jaw spasm, oral dysesthesia, dysarthria and tightness of the chest. In some cases, antihistamine and bronchodilatation agents have been administered; however, these symptoms rapidly reversed, even in the absence of any treatment. Prolonged infusion duration during the following cycles helps reduce the frequency of this syndrome.

Other neurological symptoms such as dysarthria, loss of deep tendon reflex and Lhermitte's sign were reported during treatment with oxaliplatin. Isolated cases of optic neuritis have been reported.

- Allergic reactions:

Uncommon anaphylactic reactions (in monotherapy) or common (in combination with 5-fluorouracil ± folinic acid) have been reported including cases of bronchospasms, angioedema, hypotension and anaphylactic shocks.
Common allergic reactions such as cutaneous rashes (in particular, rash followed by urticarial), conjunctivitis, and rhinitis have been reported.

- Other undesirable side effects:

Clinical ototoxicity occurs in less than1 % of patients treated with oxaliplatin. Rare cases of deafness have been reported.
Renal function disorders have been reported in about 3 % of patients, with grade 3 and 4 events in less than 1 % of patients.
Based on clinical studies and post-marketing experience, no significant ventricular arrhythmia was reported with oxaliplatin.
Frequent cases of fever have been reported: with either immune fever or infectious fever (associated or not with a neutropenia).
Rare cases of immunoallergic thrombocytopenia and hemolytic anemia have been reported.
Rare cases of acute interstitial pneumopathy and pulmonary fibrosis have been reported.
Moderate alopecia occurs in 2 % of patients treated with oxaliplatin as monotherapy; combining oxaliplatin and 5-fluorouracil does not increase the alopecia incidence observed with des 5-fluorouracil as monotherapy.
Extravasation may cause localized pain and inflammation, with potential severe implications and complications, particularly when oxaliplatin is infused via the peripheral venous system.
A transient decrease of visual acuity was reported in less than 0.1 % of patients following oxaliplatin administration.
Rare cases of dysarthria have been reported.

Irinotecan- CAMPTO® SPC extracts

DC/UNDESIRABLE EFFECTS

The following adverse reactions considered to be possibly or probably related to the administration of Irinotecan concentrate for solution for infusion have been reported from 765 patients at the recommended dose of 350 mg/m² in monotherapy, and from 145 patients treated by Irinotecan hydrochloride in combination therapy with 5FU/FA in every 2 weeks schedule at the recommended dose of 180 mg/m².

Gastrointestinal disorder:

- Delayed diarrhea:

Delayed diarrhea (occurring more than 24 hours after administration) is one of the dose-limiting toxicity of Irinotecan.

In monotherapy severe diarrhea was observed in 20 % of patients who follow recommendations for the management of diarrhea. Of the evaluable cycles, 14 % have a severe diarrhea. The median time of onset of the first liquid stool was on day 5 after the infusion of Irinotecan concentrate for solution for infusion.

In combination therapy:

- In monotherapy severe diarrhea was observed in 20 % of patients who follow recommendations for the management of diarrhea. Of the evaluable cycles, 14 % have a severe diarrhea. The median time of onset of the first liquid stool was on day 5 after the infusion of Irinotecan concentrate for solution for infusion.

In combination therapy:

- Severe diarrhea was observed in 13.1 % of patients who follow recommendations for the management of diarrhea. Of the evaluable cycles, 3.9 % have severe diarrhea.

Rare cases of pseudo-membranous colitis have been reported, one has been don't documented bacteriologically: Clostridium difficile.

- Nausea and vomiting:

- In monotherapy: severe nausea and vomiting are observed in about 10 % of patients receiving antiemetic treatment.
- In combination: decreased frequency of nausea and vomiting is observed (in 2.1 % and 2.8 % of patients, respectively).

- Dehydration: dehydration is generally associated with diarrhea and/or vomiting is reported. Renal insufficiency, hypotension or cardio-circulatory failure has been observed in patients presenting episodes of dehydration associated with diarrhea and/or vomiting.

- Other gastro-intestinal disorders: constipation relative to Irinotecan and/or loperamide has been observed in monotherapy in less than10 % of patients and, in combination, in 3.4 % of treated patients. Rare cases of intestinal obstruction, ileus or gastrointestinal hemorrhage, colitis, including typhlitis, ischemic and ulcerative colitis, and intestinal perforation. Other mild effects include anorexia, abdominal pains and mucositis.

Hematological disorders:

Neutropenia was reversible and not cumulative; the median day to nadir was 8 days whatever the use in monotherapy or in combination therapy.

In monotherapy:

- Neutropenia was observed in 78.7 % of patients and was severe (neutrophil count < 500 cells/mm3) in 22.6 % of patients. Of the evaluable cycles, 18 % had a neutrophil count below 1,000 cells/mm³ including 7.6 % with a neutrophil count < 500 cells/mm³. Total recovery was usually reached by day 22. Fever with severe neutropenia was reported in 6.2 % of patients and in 1.7 % of cycles. Infectious episodes occurred in about 10.3 % of patients (2.5 % of cycles) and were associated with severe neutropenia in about 5.3 % of patients (1.1 % of cycles), and resulted in death in 2 cases. Anemia was reported in about 58.7 % of patients (8 % with hemoglobin < 8 g/dl and 0.9 % with hemoglobin < 6.5 g/dl). Thrombocytopenia (< 100,000 cells/mm3) was observed in 7.4 % of patients and 1.8 % of cycles with 0.9 % with platelets ≤ 50,000 cells/mm3 and 0.2 % of cycles. Nearly all the patients showed a recovery by day 22.

In combination:

- Neutropenia was observed in 82.5 % of patients and was severe (neutrophil count < 500 cells/mm3) in 9.8 % of patients. Of the evaluable cycles, 67.3 % had a neutrophil count below 1,000 cells/mm³ including 2.7 % with a neutrophil count < 500 cells/mm³. Total recovery was usually reached within 7-8 days. Fever with severe neutropenia was reported in 3.4 % of patients and in 0.9 % of cycles. Infectious episodes occurred in about 2 % of patients (0.5 % of cycles) and were associated with severe neutropenia in about 2.1 % of patients (0.5 % of cycles), and resulted in death in 1 case. Anemia was reported in 97.2 % of patients (2.1 % with hemoglobin < 8 g/dl). Thrombocytopenia 100,000 cells/mm³) was observed in 32.6 % of patients and 21.8 % cycles. No severe thrombocytopenia (< 50,000 cells/mm³) has been observed.

One case of peripheral thrombocytopenia with antiplatelet antibodies has been reported in the post-marketing experience.

Infection:

Renal insufficiency, hypotension or cardio-circulatory failures have been observed in patients who experienced sepsis.

General disorders and administration site reaction:

- Severe transient acute cholinergic syndrome (The main symptoms were defined as early diarrhea and various other symptoms such as abdominal pain, conjunctivitis, rhinitis, hypotension, vasodilatation, sweating, chills, malaise, dizziness, visual disturbances, miosis, lacrimation and increased salivation)

- *Acute cholinergic syndrome*: commonly severe transient acute cholinergic syndrome, transient is observed in 9 % of patients treated with monotherapy and 1.4 % of patients treated with combination chemotherapy. The main symptoms were defined as early diarrhea and various other symptoms such as abdominal pain, conjunctivitis, rhinitis, hypotension, vasodilatation, sweating, chills, malaise, dizziness, visual disturbances, mitosis, lacrimation and increased salivation occurring during or within the first 24 hours after the infusion of Irinotecan concentrate for solution for infusion. These symptoms disappear after atropine administration

- Severe asthenia has been observed in less than 10 % of patients treated with monotherapy and 6.2 % of treated with combination chemotherapy. Attribution to Irinotecan is not clearly established. Isolated fever in the absence of infection and without concomitant severe neutropenia has occurred in 12 % of patients in monotherapy and 6.2 % of patients in combination chemotherapy. Moderate reactions at the site of injection are uncommon.

- Cardiovascular disorders: rare cases of hypertension during or following infusion.

- Respiratory disorders: rare cases of interstitial pneumopathy and pneumonitis with pulmonary infiltrates and early effects such as dyspnea.

- Cutaneous and sub-cutaneous disorders: reversible alopecia is very common. Cutaneous reactions are of moderate intensity and uncommon.

- Immune system disorders: allergic reactions of moderate intensity are uncommon, rare cases of anaphylactic/anaphylactoid reactions have been reported.

- Musculo-skeletal disorders: early effects such as muscular spasms contraction or cramps and paresthesia have been reported.

Investigations: *In monotherapy*, transient and mild to moderate increases in serum levels of either transaminases, alkaline phosphatase or bilirubin were observed, in 9.2%, 8.1% and 1.8% of patients, respectively, in the absence of progressive liver metastasis. Transient and mild to moderate increases of serum levels of creatinine was observed in 7.3% of patients.

In combination therapy transient serum levels (grade 1 and 2) of serum transaminases (ALAT and ASAT), alkaline phosphatase or bilirubin were observed, in 15%, 11% and 10% of patients, respectively, in the absence of progressive liver metastasis.

Transient grade 3 cases have been observed in 0 %, 0 %, 0 % and 1 % of patients, respectively. No grade 4 cases were observed. In very rare cases, increases of serum amylase and/or serum lipase have been reported. Hypokalemia mainly related to diarrhea and vomiting are also very rare.

Nervous system disorder: very rare transient cases of speech disorder have reported during Irinotecan infusion.

5 Fluorouracil - SPC extracts

DC/UNDESIRABLE EFFECTS

Stomatitis, Mucositis, Diarrhea, Anorexia, Nausea, Vomiting, Digestive hemorrhage (extremely rare), Skin pigmentation, Alopecia, Dermatitis, Cutaneous eruption, Urticarial reactions, Photosensitivity (sun allergy), Precordial pain, Electrocardiogram abnormalities, Myocardial infarction (extremely rare), Leucopenia, Thrombocytopenia, Anemia (rare), Ataxia, Lacrimation.

Folinic acid - SPC extracts

DC/UNDESIRABLE EFFECT

They depend on the dose injected and the administration schedule of 5-fluorouracil:

diarrhea: in elderly patients, risk of dehydration (see SPC - Special Warnings and Precautions for Use); mucositis, stomatitis (see SCP - Special Warnings and Precautions for Use); cutaneous reactions: dry skin, erythema; conjunctivitis, lacrimation; moderate hematological toxicity.

Gemcitabine – GEMZAR® - SPC extracts

DC/UNDESIRABLE EFFECT

- Hematologic: gemcitabine may induce medullar aplasia, resulting in aplasia, leucopenia and thrombocytopenia. Myelosuppression is usually moderate; it is however more pronounced for granulocytes. Thrombocythemia is also commonly reported.

- Hepatobiliary: Transient increases in hepatic transaminases are observed, usually low and not requiring treatment discontinuation. However, caution must be used in patients with altered liver function.

- Esophogastrointestinal: Nausea, sometimes with vomiting. These side effects require therapeutic management in about 20 % of cases. They can be easily treated with standard antiemetic agents and rarely require gemcitabine dose adaptation. Diarrhea, and mouth toxicity such as mucositis.

- Pulmonary: within hours following gemcitabine infusion, patients may present dyspnea, generally weak and short-lasting. They seldom require posology adjustment and are usually reversed without specific treatment. The mechanism of this toxicity is unknown. Severe rarely fatal pulmonary effects, such as pulmonary edema, interstitial pneumonitis and acute respiratory distress syndrome (ARDS) have been reported as less common or rare. In such cases, gemcitabine treatment must be stopped. Steroids may relieve the symptoms in such situations. Starting supportive treatment at an early stage may improve the situation.

- Renal: Moderate proteinuria and hematuria occur in about half of patients, but are rarely clinically significant; these side effects are usually not associated with modifications of serum creatinine or uremia. However, a few cases of renal insufficiency of unclear etiology have been reported. No cumulative renal toxicity has been observed (see *SPC* - Special Warnings and Precautions for Use). Clinical manifestations compatible with the uremic hemolytic syndrome have been reported in patients receiving gemcitabine. Gemcitabine must be discontinued as soon as the first signs of microangiopathic hemolytic anemia such as a sudden drop in hemoglobin with concomitant thrombocytopenia, an elevation of serum bilirubin, serum creatinine, blood level of urea or LDH. Renal insufficiency may not be reversed, even after treatment discontinuation. In such case, dialysis may become necessary.

- Allergic reactions: eruptions with pruritis may occur, usually weak; they do not require dose reduction and respond to local treatment. Peeling, vesiculation and ulceration are secondary side effects occasionally reported. Cases of bronchospasm are sometimes reported. Usually transient and moderate, these cases may require parenteral treatment. Gemcitabine must not be administered to patients with known hypersensitivity to this product. Rare cases of anaphylactic reactions have been reported.

- Cardiac: very rare cases of Myocardial infarction, congestive heart failure, arrhythmia - predominantly supraventricular in nature and a few cases of hypotension have been reported.

- Cutaneous: with the concurrent use of gemcitabine and radiotherapy, severe musculocutaneous symptoms such as dermatopolymyositis, closely related to the site previously irradiated, have been reported.

- Others: a rarely severe influenza syndrome may occur. It is usually of short duration and does not require a dose reduction. Fever, headache, back pain, chills, myalgia, asthenia and anorexia are the most common symptoms. Coughing, rhinitis ; dizziness, sweating and insomnia are currently observed. Fever and asthenia are sometimes isolated symptoms.The mechanism of this toxicity remains unknown. Paracetamol may attenuate the symptoms.
Peripheral edema and very rarely edema of the face: peripheral edema is usually moderate and requires dose reduction only very rarely. However, it can be painful. It is usually reversed after gemcitabine

discontinuation. The mechanism of this toxicity is unknown. It is not associated with signs of cardiac, hepatic or renal insufficiency. Other secondary side effects commonly reported are: alopecia (usually minimal), drowsiness.

APPENDIX 14 :
Translational research

A prerequisite to better manage a disease is to gain knowledge on the biological mechanisms associated with it.

Biomarkers are indicators of normal or pathological biological processes that may be related to the disease prognosis or response/resistance to therapeutic interventions.

In the present study, blood and tumor samples will be collected to carry out pharmacogenetic and pharmacogenomic studies.

STUDY DESCRIPTION

1 – Study of tumor characteristics

Conservation of tissue samples, frozen or embedded in paraffin blocks (ADN, proteins), for future research and to identify the risk of early metastasis via genomics or proteomic studies.

2- Study of polymorphic variants
For each individual patient, characteristics that are potentially predictive of treatment efficacy and toxicity will be evaluated (using a venous blood sample).

- DPD with respect to the hematological toxicity of 5FU,
- ERCC1 with respect to response to oxaliplatin,
- UGT1A1 with respect to response to irinotecan,
- CDA (cytidine deaminase) with respect to the toxicity and therapeutic efficacy of gemcitabine (FFCD 1004-PRODIGE study, conducted in parallel)

Polymorphic variants evaluation on SNP Illumina chips, within the program of the Groupe de Pharmacologie Clinique Oncologique of UNICANCERUNICANCER

THIS STUDY WILL ALLOW:

- a large number of patients to be evaluated, with the determination of constitutional and tumoral factors that are most discriminating in predicting toxicity and response to treatment.

- the mechanisms of sensibility and resistance to treatments to be understood better and will constitute a better approach towards a targeted treatment. Ultimately, at the end of the study, the goal is to offer individualized treatment to each patient according to genetic and epigenetic factors that are relevant to predict efficacy and toxicity of chemotherapy.

SAMPLE TAKING AND STORAGE:

1 – Tumor sample study

Tumor tissue sample

After the patient has been informed and has given signed consent to participate in the translational study, paraffin blocks containing tumor tissue samples will be collected.
No additional invasive medical intervention will be required. The samples used in the translational study will

be collected from tumor tissues that have been already used for the pancreatic cancer diagnosis. Ideally, the samples will be collected at the beginning of the study, at the same as other samples are collected for the translational research. However, they may be collected later on during the study.

2 – Pharmacogenetic study

The pharmacogenetic study is aimed at identifying genetic factors associated with the disease prognosis as well as the tolerance and efficacy of the evaluated treatment.

Blood samples

After the informed consent form has been signed by the patient, a blood sample will be collected from a venous blood puncture performed during medical care/examination necessary for the patient. In no circumstance, the pharmacogenetic study will require other blood tests than those already scheduled in the treatment protocol. DNA will be extracted from 10 ml of peripheral venous blood (2 EDTA spray-coated blood tubes of 5 ml, i.e. 10 ml in total) for the genetic polymorphism study.

Every time a patient is included in the Prodige 24/Accord24 study, the randomization service will send by Fax a copy of the randomization sheet indicating whether the patient has accepted to give a blood sample for the pharmacogenetic study. In this case, a mail will be sent to the clinical investigator of the centre which has included the patient, with a pre-paid shipment box to be used for the transport of the collected biological materials.

On the same day, the center will send the 2 blood test tubes enclosed in a DHL envelop.

Warning: test tubes containing samples must be conserved in a refrigerator before they are sent to the center for translational study (shipment and mailing procedures must be in conformity with the regulation on blood and biological samples).

PRODIGE 24/PA-6 – PROTOCOL AMENDMENTS

Version	Summary of Changes
Protocol v2.1 04/08/2011	Original
Protocol v3 16/11/2011	1. Administrative changes
Protocol v4 13/05/2012	1. Precision on resection margins 2. Modification in the flow chart to be in conformity with the protocol
Protocol v5 03/04/2013	1. Precision in the inclusion and exclusion criteria 2. Precision to the patient follow-up period for the patients 3. Administrative changes.
Protocol v6 20/06/2014	1. Reduction of the dose of irinotecan following the IDMC held on the 12/03/2014 2. Modification of the maximum delay between pancreatectomy and inclusion following the publication of Valle JW et al. in the J Clin Oncol 2014;32:504-12. 3. Modification of the recommendation for the prevention of neurotoxicities following a publication in the JCO (C.L. Loprinzi et al., JCO 2013) 4. Updated study contacts.
Protocol v7 02/02/2015	1. Prolongation of the inclusion period 2. Modification in the flow chart to be in conformity with the protocol 3. Confirmation of the reduction of irinotecan dose not modified in the protocol v6 after the previous amendment

Biometrics Unit
CTD labelled by INCa

Statistical Analysis Plan

PROTOCOL PRODIGE 24
N° EudraCT : 2011-002026-52

PHASE III TRIAL COMPARING ADJUVANT CHEMOTHERAPY WITH GEMCITABINE VERSUS 5-FLUOROURACIL, LEUCOVORIN, IRINOTECAN AND OXALIPLATIN (MFOLFIRINOX) IN PATIENTS WITH RESECTED PANCREATIC ADENOCARCINOMA

Edition n° 3 of 17/02/2022

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Protocol number:	2011-002026-52
Protocol version	Protocol V°7 of the 2nd February 2015
Study Phase :	III
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VERSION n°	**Date**	**Author**	**Reason**
1	24/07/2017	FC	Creation / Translation SAP French >>English
2	20/07/2021	FC	SAP template Addition of section 5.3.5: Additional analyses
3	17/02/2022	FC	5.3.5. Additional analysis/ Addition of exploratory data analysis for manuscript submission

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ABREVIATIONS LIST

AE	Adverse Event
BMI	Body Mass Index
BSA	Body Surface Area
CI	Confidence Interval
CD	Cumulative Dose
CPP	Comité de Protection des Personnes (French Ethics Committee)
D	Day
DFS	Disease-Free Survival
DI	Dose Intensity
DSMB	Data and Safety Monitoring Board
FFCD	Fédération Francophone de Cancérologie Digestive
5-FU	5-Fluorouracil
H	Hour
HR	Hazard Ratio
IC	Inclusion Criteria
ICH	International Conference on Harmonisation
ITT	Intent To Treat
MFS	Metastasis-Free Survival
mITT	Modified Intent To Treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NIC	Non-Inclusion Criteria
OS	Overall Survival
OSr	Overall Survival from first recurrence
RDI	Relative Dose Intensity
SAE	Severe Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SS	Specific Survival
WHO	World Health Organization

The Statistical Analysis Plan (SAP) describes the statistical analyses to be performed for the study Prodige 24/ACCORD24.

This SAP was written from the following documents:

- Original protocol containing all the amendments
- International Conference on Harmonisation (ICH) guideline E9 (Statistical Principles for Clinical Trials)
- Guidelines for the Content of Statistical Analysis Plans in Clinical Trials (*JAMA*. 2017;318(23):2337-2343. doi:10.1001/jama.2017.18556)
- Reporting guidelines for main study types (http://www.equator-network.org/)
  - CONSORT : Randomized trials

1. SYNOPSIS

Source of synopsis: Extract of synopsis from Protocol V°7 of the 2nd February 2015

A) IDENTIFICATION DE L'ESSAI CLINIQUE	
NUMERO DE CODE PROMOTEUR : UC-0110/1006 PRODIGE 24 – ACCORD 24 **VERSION ET DATE :** VERSION N°6 DU 20/06/2014	
TITRE DE L'ESSAI : Essai randomisé de phase III multicentrique comparant une chimiothérapie adjuvante de 6 mois par Gemcitabine versus une association de 5-Fluorouracile, Irinotécan et Oxaliplatine (mFolfirinox) chez des patients opérés d'un adénocarcinome pancréatique.	
TITRE ABREGE : NA	
COORDONNATEUR : Pr Thierry CONROY, oncologue médical (UNICANCER, Nancy) **CO-COORDONNATEUR :** Pr Patrick RAT, chirurgien (FFCD, Dijon)	
NOMBRE DE CENTRES ESTIMES : 40	**NOMBRE DE PATIENTS :** 490

B) IDENTIFICATION DU PROMOTEUR
NOM DE L'ORGANISME : UNICANCER
PERSONNE A CONTACTER :Trevor STANBURY Adresse : R&D UNICANCER 101 rue de Tolbiac - 75654 PARIS CEDEX 13 Tel : 01.44.23.55.67 - Fax : 01.44.23.04.69 t-stanbury@unicancer.fr

C) INFORMATION GENERALE SUR L'ESSAI
INDICATION : Adénocarcinome du pancréas exocrine
METHODOLOGIE : Essai national multicentrique, de phase III de supériorité, comparant une chimiothérapie adjuvante standard par gemcitabine à un bras expérimental utilisant une polychimiothérapie par mFolfirinox
OBJECTIF PRINCIPAL : Comparer la survie sans maladie à 3 ans entre les 2 bras.
OBJECTIF(S) SECONDAIRE(S) : • Survie globale et survie spécifique • Survie sans métastase • Evaluer la toxicité selon la classification NCI-CTCAE v4.0 • Etude ancillaire, translationnelle (optionnelle).

CRITERES D'INCLUSION :

Tous les critères sont nécessaires pour l'inclusion :

1. Adénocarcinome canalaire du pancréas histologiquement prouvé (les TIPMP avec composante invasive sont éligibles)
2. Résection macroscopiquement complète (exérèse R0 ou R1).
3. Patient de 18 à 79 ans.
4. Etat général : OMS 0-1
5. Pas de radiothérapie ni de chimiothérapie antérieure.
6. Récupération postopératoire satisfaisante et patient en état de supporter une chimiothérapie : pas de vomissements significatifs et apport calorique ≥ 1500 calories/jour.
7. Fonction hématologique satisfaisante (PNN ≥ 1500/mm^3, plaquettes ≥ 100 000/mm^3, et hémoglobine ≥ 10 g/dL - éventuellement après transfusions sanguines).
8. Bilirubine ≤ 1,5 fois la limite supérieure de la normale.
9. Clairance calculée ≥ 50 mL/min.
10. Contraception adéquate pour les hommes, et pour les femmes non ménopausées. Les patients en âge de procréer doivent accepter d'utiliser deux méthodes de contraception validées médicalement (une pour le patient et l'autre pour le partenaire) durant l'étude et durant les 6 mois pour les hommes et 4 mois pour les femmes suivant la dernière prise de traitement (les femmes ne pourront entrer dans l'étude qu'après un test de grosses négatif).
11. Intervalle depuis la pancréatectomie entre 21 et 84 jours.
12. Information du patient et signature du consentement éclairé.
13. Affiliation à un régime de sécurité sociale

CRITERES DE NON INCLUSION :

Un seul critère est suffisant pour la non inclusion :

1. Autre type de tumeur du pancréas non canalaire, en particulier tumeur endocrine ou adénocarcinome à cellules acineuses, cystadénocarcinome ou ampullome malin.
2. Présence de métastases (y compris ascite ou pleurésie maligne).
3. Présence de résidu macroscopique (exérèse R2)
4. CA 19-9 > 180 U/ml à l'inclusion (dosage à effectuer au moins 21 jours après l'opération)
5. Insuffisance cardiaque ou insuffisance coronarienne symptomatique.
6. Comorbidité majeure susceptible d'empêcher la délivrance du traitement ou infection évolutive active (HIV ou hépatite chronique B ou C) ou diabète incontrôlable.
7. Neuropathie préexistante, maladie de Gilbert ou génotype UGT1A1*28/*28 connu.
8. Maladie inflammatoire du côlon ou du rectum, ou occlusion ou sub-occlusion, ou diarrhée sévère postopératoire non contrôlée.
9. Autre cancer concomitant, ou antécédent de cancer en dehors d'un cancer in situ du col utérin ou d'un carcinome basocellulaire ou spinocellulaire correctement traité.
10. Intolérance héréditaire au fructose
11. Personnes privées de liberté ou sous tutelle.
12. Impossibilité de se soumettre au suivi médical de l'essai pour des raisons géographiques, sociales ou psychologiques.

CRITERE D'EVALUATION PRINCIPAL : survie sans maladie à 3 ans

RANDOMISATION :

La randomisation sera stratifiée et réalisée sur les facteurs suivants :

- le centre
- le statut ganglionnaire pN0 (< 12 ganglions examinés versus ≥12 ganglions examinés) versus pN1
- le statut des marges chirurgicales : R0 versus R1
- CA19-9 à l'inclusion ≤ 90 versus CA19-9 entre 91 et 180 U/ml

D) DESCRIPTION DES MEDICAMENTS EXPERIMENTAUX

MEDICAMENTS :

Nom du médicament (DCI)	Nom de la Spécialité (1)	Forme pharmaceutique	Voie d'administration	Posologie par administration
Gemcitabine	Gemzar®	Poudre pour solution injectable	IV	**1000 mg/m²** en 30 minutes 3 semaines sur 4 (= 1 cycle) pendant 6 cycles, soit 24 semaines.

Nom du médicament (DCI)	Nom de la Spécialité(1)	Forme pharmaceutique	Voie d'administration	Posologie par administration
Acide Folinique	-	Poudre pour solution injectable	IV	**400 mg/m²**, en perfusion de 2 heures

Nom du médicament (DCI)	Nom de la spécialité(1)	Forme pharmaceutique	Voie d'administration	Posologie par administration
irinotécan	Campto®	Solution à diluer pour perfusion	IV	**150 mg/m²** J1 en 90 minutes débutant 30 min après le début de l'acide folinique

Nom du médicament (DCI)	Nom de la spécialité(1)	Forme pharmaceutique	Voie d'administration	Posologie par administration
5Fluorouracile	-	poudre pour solution injectable	IV	**2,4 g/m²** en perfusion continue sur 48 h (1200 mg/m²/ jour)

Nom du médicament (DCI)	Nom de la spécialité(1)	Forme pharmaceutique	Voie d'administration	Posologie par administration
oxaliplatine	Eloxatine® ou générique	Solution à diluer pour perfusion Ou poudre	IV	**85 mg/m²** J1 en 2 heures

(1) Dans le cas de médicament générique, indiquer uniquement la DCI, la spécialité est laissée au choix du centre investigateur.

SCHEMA THERAPEUTIQUE :
Les patients ayant signé leur consentement et répondant à tous les critères d'inclusion et de non-inclusion seront randomisés soit dans le Bras A, soit dans le bras B:

Bras A : Gemcitabine 1000 mg/m² en 30 minutes, une fois par semaine, 3 semaines sur 4 (= 1 cycle) pendant 6 cycles, soit 24 semaines.
Bras B : mFolfirinox tous les 14 jours, 12 cycles, soit 24 semaines

mFolfirinox :
oxaliplatine (Eloxatine®) 85 mg/m² J1 en 2 heures, puis
irinotécan (Campto®) 150 mg/m² J1 en 90 minutes débutant 30 min après le début de l'acide folinique
acide folinique 400 mg/m² (racémique) (ou 200 mg/m² si acide L-folinique), en perfusion de 2 heures en Y de l'oxaliplatine
5-FU IV en perfusion continue 2,4 g/m² sur 48 heures (1200 mg/m²/ jour)

DUREE DE TRAITEMENT : 24 semaines

E) CONSIDERATIONS STATISTIQUES

CALCUL DU NOMBRE DE SUJETS NECESSAIRES :

Le nombre total de patients randomisés sera de 490 afin d'obtenir les 342 événements nécessaires. Une randomisation 1 :1 par minimisation sera réalisée sur les facteurs de stratification suivants: centre, statut ganglionnaire pN0 (< 12 ganglions examinés versus ≥12 ganglions examinés) versus pN1 ; résection R0 versus R1 ; CA 19-9 à l'inclusion ≤ 90 versus CA 19-9 entre 91 et 180 U/mL.
Une analyse précoce de la tolérance est planifiée après les 30 premiers patients inclus (des 2 premiers cycles), pour s'assurer que le taux de diarrhée de grade 3-4 ne dépasse pas 5% des patients, sans quoi la dose d'irinotécan sera réduite à 150 mg/m^2
Une analyse intermédiaire sur le critère principal est planifiée après l'observation de 113 événements.
Une règle d'arrêt précoce pour un taux de décès toxique > 2% est planifiée.

METHODE D'ANALYSE STATISTIQUE :

L'analyse statistique sera détaillée dans le plan d'analyse statistique (élaboré avant le premier gel de la base de données pour l'analyse intermédiaire).
Les variables qualitatives seront présentées par les fréquences et pourcentages de chaque modalité et comparées entre les groupes par le test de chi-2. Les variables quantitatives seront présentées par des moyennes, écart-types, médianes et étendues. Elles seront comparées entre les groupes par le test T de Student ou de Kruskal-Wallis selon les conditions d'application. Les grades de toxicité entre les groupes seront comparés par le test non paramétrique de Kruskal-Wallis. La survie sans maladie sera définie comme le délai entre la randomisation et la survenue du premier événement tels que la rechute locale, métastatique, la survenue d'un second cancer ou le décès quelle qu'en soit la cause. L'effet relatif du traitement dans le bras expérimental sera présenté par le hazard ratio et l'intervalle de confiance à 95 %. Les facteurs pronostiques de récidive seront évalués par le modèle de Cox. Les analyses seront réalisées en intention de traiter.

F) MATERIELS BIOLOGIQUES COLLECTES POUR LA RBM

TYPES D'ECHANTILLON(S) : Tumeurs et sang

QUANTITE COLLECTEE : 10 ML

G) DUREE PREVUE DE L'ESSAI

PERIODE D'INCLUSION : 5 ans

PERIODE DE TRAITEMENT : 24 semaines

PERIODE DE SUIVI : 5 ans

DUREE ENVISAGEE JUSQU'A L'ANALYSE DE L'OBJECTIF PRINCIPAL : 8 ans

DUREE GLOBALE DE L'ESSAI (PERIODE DE SUIVI INCLUSE) : 10 ans

H) TABLEAU RECAPITULATIF DES INVESTIGATIONS

Bras A = 6 mois de traitement

Plan de surveillance BRAS A gemcitabine

Visite	Bilan inclusion	Bilans de suivi					Bilan 3 mois	Bilans de suivi							Suivi après traitement (4)
N° de visite (V)	V0	V1,2,3	V4	V5,6,7	V8	V9,10,11	V12	V13, 14,15	V16	V17 18, 19	V20	V21, 22, 23	V24	VF entre 2 et 4Sem	
Date	J0	J1, J8, J15	J22	J29, J36, J43	J50	J57, J64, J71	J78	J85, J92, J99	J106	J113, J120, J127	J134	J141, J148, J155	J162	Entre J 183 et J 196	
Consentement éclairé signé	X														
Critères d'inclusion / non inclusion	X														
Randomisation	X														
Examen clinique															
Poids	X			X		X	X	X		X		X		X	X
Taille	X						X							X	X
Etat général OMS	X	X		X		X	X	X		X		X		X	X
Examen neurologique	X													X	X
Traitements concomitants	X														
Toxicités (2)															
Evaluation de la tolérance		X J8 et J15		X		X	X	X		X		X		X	X
Examen Biologique (3)															
NFS, plaquettes	X	X		X		X		X		X		X			
Calcémie	X														
Ionogramme	X	X		X		X		X		X		X			
Protidémie	X	X		X		X		X		X		X			
Albuminémie	X														
Bilan hépatique	X*	X**		X**		X**		X**		X**		X**			
Créatininémie	X														
Clairance à la créatinine calculée	X														
Glycémie	X	X		X		X		X		X		X			
Ca 19-9	X						X							X	X
Test de grossesse	X(1)														
Bilan paraclinique (5)															
Scanner TAP (6)	X						X							X	X
ECG	X														
Recherche Translationnelle															
Récupération de biopsies de diagnostic	X														
Prélèvement sanguin 10 mL sur EDTA (2 x 5 ml)	X														

* *Bilan hépatique : phosphatases alcalines, bilirubine totale, libre et conjuguée, ALAT et ASAT*

** *Bilan hépatique avec bilirubine totale, libre et conjuguée, ALAT et ASAT*

(1) pour les femmes en âge de procréer

(2) Evénements Indésirables Graves (EIG) à déclarer dans les 48 heures au promoteur jusqu'à 30 jours après la fin de la dernière cure de chimiothérapie. Au-delà de cette période seuls les EIG susceptibles d'être dus à la recherche seront déclarés au promoteur dès lors qu'aucune autre cause que la recherche ne peut raisonnablement être attribuée.

(3) Le bilan biologique à l'inclusion doit être effectué dans un délai maximal de 7 jours précédant la randomisation et un délai de max 84 jours après la chirurgie.

(4) **A compter de la VF (qui a lieu entre deux et quatre semaines après la fin du dernier cycle de chimiothérapie): tous les 3 mois durant les 2 premières années puis tous les 6 mois pendant 3 ans.**

(5) Les examens paracliniques d'inclusion doivent être effectués dans un délai maximal de 30 jours précédant la randomisation et un délai de max 84 jours après la chirurgie.

(6) Ou IRM abdomino-pelvienne et scanner thoracique en cas d'allergie au produit de contraste.

Les patients ayant progressé seront suivis tous les 6 mois jusqu'au décès. Seront évalués : les effets toxiques à long terme et la survie. Si un autre traitement est établi, il devra être rapporté.

Bras B
12 cycles prévus = 6 mois de traitement

Plan de surveillance BRAS B mFolfirinox															
Visite	**Bilan inclusion**	**Bilans de suivi tous les 14 jours**							**Bilan 3 mois**	**Bilans de suivi tous les 14 jours**					**Suivi après traitement (4)**
N°de visite	**V0**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**VF entre 2 et 4 sem**	
Consentement éclairé signé	X														
Critères d'inclusion / non inclusion	X														
Randomisation	X														
Examen clinique															
Poids	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Taille	X								X					X	X
Etat général / OMS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Examen neurologique														X	X
Traitements concomitants	X														
Toxicités (2)															
Evaluation de la tolérance			X	X	X	X	X	X	X	X	X	X	X	X	X
Examen biologique (3)															
NFS, plaquettes	X	X	X	X	X	X	X	X	X	X	X	X	X		
Calcémie															
Ionogramme	X	X	X	X	X	X	X	X	X	X	X	X	X		
Protidémie	X	X	X	X	X	X	X	X	X	X	X	X	X		
Albuminémie	X														
Bilan hépatique	X*	X**	X**	X**	X**	X**	X**	X**	X**	X**	X**	X**	X**		
Créatininémie	X	X													
Clairance à la créatinine calculée	X														
Glycémie	X	X	X	X	X	X	X	X	X	X	X	X	X		
CA 19-9	X								X					X	X
Test de grossesse	X(1)														
Bilan paraclinique (5)															
Scanner TAP (6)	X								X					X	X
ECG	X														
Recherche Translationnelle															
Récupération de biopsies de diagnostic	X														
Prélèvement sanguin 10 mL sur EDTA (2 x 5 ml)	X														

* *Bilan hépatique : phosphatases alcalines, bilirubine totale, libre et conjuguée, ALAT et ASAT*
** *Bilan hépatique avec bilirubine totale, libre et conjuguée, ALAT et ASAT*
(1) pour les femmes en âge de procréer
(2) Evénements Indésirables Graves (EIG) à déclarer dans les 48 heures au promoteur jusqu'à 30 jours après la fin de la dernière cure de chimiothérapie. Au-delà de cette période seuls les EIG susceptibles d'être dus à la recherche seront déclarés au promoteur dès lors qu'aucune autre cause que la recherche ne peut raisonnablement être attribuée.
(3) Le bilan biologique à l'inclusion doit être effectué dans un délai maximal de 7 jours précédant la randomisation et un délai de max 84 jours après la chirurgie.
(4) **A compter de la VF (qui a lieu entre deux et quatre semaines après la fin du dernier cycle de chimiothérapie): tous les 3 mois durant les 2 premières années puis tous les 6 mois pendant 3 ans.**
5) Les examens paracliniques d'inclusion doivent être effectués dans un délai maximal de 30 jours précédant la randomisation et un délai de max 84 jours après la chirurgie.
(6) Ou IRM abdomino-pelvienne et scanner thoracique en cas d'allergie au produit de contraste.

Les patients ayant progressé seront suivis tous les 6 mois jusqu'au décès. Seront évalués : les effets toxiques à long terme et la survie. Si un autre traitement est établi, il devra être rapporté.

2. ENDPOINTS

2.1 PRIMARY ENDPOINT

Disease-free survival (DFS) is defined as the interval between randomization and the occurrence of the first observed oncologic event, such as, local or metastatic recurrence, second cancer, or death from any cause. Patients without events at the time of analysis will be censored on the date of the last informative follow-up.

Disease-free survival (DFS DATECAN) **according to DATECAN initiative** is defined as the interval between randomization and the occurrence of the first observed oncologic event, such as, local or metastatic recurrence, pancreatic second cancer or death from any cause. The difference between these definitions is that second non-pancreatic cancers are not included as events in the DATECAN definition. The analysis of disease-free survival according to the DATECAN definition will also be performed.

2.2 SECONDARY ENDPOINTS

Overall survival (OS) is defined as the interval between the randomization and the occurrence of death whatever the cause. Patients alive at the time of the analysis will be censored on the date of the last informative follow-up.

Specific survival (SS) is defined as the interval between the randomization and the occurrence of death due to cancer or to a treatment-related toxicity.

Metastasis-Free Survival (MFS) is defined as the interval between the randomization and the occurrence of the first distant event at all sites of recurrence other than the resection site (e.g. peritoneal, hepatic, pulmonary or lymph node) or death whatever the cause. Loco-regional events will be ignored and patients alive without metastases at the time of analysis will be censored at the time of the last review not targeting this type of event.

Toxicity is assessed according to the NCI-CTCAE version 4.0 toxicity scale.

The definitions of time to event endpoints are summarized in Table 1.

Table 1 : Definition of time to event endpoints

	Population*	Events	Date of event	Censoring	Date of censoring
DFS	ITT	Local relapse Metastasis Second cancer Death	Date of 1st event	Alive without event	Date of latest news
DFS-DATECAN	ITT	Local relapse Metastasis Pancreatic second cancer Death	Date of 1st event	Alive without event	Date of latest news
OS	ITT	Death	Date of death	Alive	Date of latest news
SS	ITT	Death due to cancer or related treatment toxicity	Date of death	Alive Death other reason	Date of latest news
MFS	ITT	Metastasis Death	Date of 1st event	Alive without métastasis	Date of latest news

*cf. next page for the definition of populations

3. PLANNED ANALYSES

Table 2 : Listing of planned analyses

Analysis	Objective	Criteria	Planned schedule	
DSMB	Toxicity evaluation	Rate of grade 3-4 diarrhea <5%	n=30 patients Arm B	March 2014
Intermediate	Efficacy analysis	DFS	113 events	December 2015
Final	Efficacy analysis	DFS	342 events	2018

4. DEFINITION OF POPULATIONS

Intent-to-Treat Population (ITT): randomized patients, whether or not treated, eligible or not. Patients are analyzed in the assigned arm by randomization.

Modified Intent-to-Treat Population (mITT): all patients without violation of major inclusion or non-inclusion criteria. The major inclusion (IC) and non-inclusion criteria (NIC) are listed below:

- IC n°2: Macroscopically complete resection (R0 or R1 resection)
- IC n°7: Adequate hematologic function (ANC ≥1500/mm3, platelets ≥100 000/mm3 and hemoglobin ≥ 10 g/L – [possibly after transfusion]).
- IC n°8: Adequate liver function (bilirubin ≤ 1.5 times the institutional upper limit of normal)

- NIC n°2: Metastasis (including ascitis or malignant pleural effusion)
- NIC n°3: Presence of macroscopic tumor residues (R2 resection)
- NIC n°4: CA 19-9> 180 U/mL at inclusion (dosage to be performed at least 21 days after surgery)
- NIC n°5: Heart failure or coronary heart disease symptoms
- NIC n°6: Major comorbidity that may preclude the delivery of treatment or active infection (HIV or chronic hepatitis B or C) or uncontrolled diabetes

Safety population: all patients who received at least one dose of treatment. Patients will be analyzed in the treatment arm they actually received

All statistical analyzes will be performed on the ITT population. Tolerance analysis will be performed on the safety population.

5. MATERIAL AND METHODS

5.1 DEFINITION AND CONVENTIONS

Time to events will be calculated from the date of randomization.

For any calculation of time between two dates, the following convention will be applied: **[later date] – [earlier date].**

For any calculation of duration between two dates, the following convention will be applied: **[later date] – [earlier date] + 1 jour.**

To convert a number of days to year or month, the following convention will be applied:

1 year = 365.25 days;
1 month = 30.4375 days.

Day 1 (D1) of the cycle is defined as the date of the first administration of the Cycle.

Date of discontinuation is defined as the last day the subject receives a study treatment.

5.2 MATERIAL

5.2.1 Subject disposition

The following will be summarized:
- Distribution of patients by center (overall and by arm)
- Patients disposition: ITT population, modified ITT population, safety population (overall and by arm)
- CONSORT flowchart

5.2.2 Stratification factors

Stratification factors used in randomization will be described:
- Center
- Nodes status pN0 (<12 retrieved nodes *versus* ≥12 retrieved nodes) *versus* pN1
- Resection margin R0 *versus* R1
- Baseline CA19-9 : ≤ 90 U/mL *versus* between 91-180 U/mL

5.2.3 Baseline characteristics

Baseline characteristics include demographic data (age, gender, WHO performance status, usual weight, weight, height, body surface area (BSA), Body Mass Index (BMI), history of the disease (surgery and pathology), laboratory data, clinical examination, paraclinical, comorbidities.

Derived variables are presented in the following table:

Table 3 : Dirived variables for baseline characteristics

Calculated variable	Formula
Age	int((date of inclusion – date of birth) / 365.25)
Body mass index (BMI)	BMI= weight / (height in m)² 4 categories : underweight <18,5 / normal<25 / overweight<30 / obese≥30
Body surface area (BSA)	Dubois & Dubois formula: BSA = (weight in kg) $^{0.425}$ * (height in m) $^{0.725}$ * 0.20247

5.2.4 Treatments administration

Treatment administration will be described by patient.

Chemotherapy:

Variables characterizing treatment administration will be calculated and presented for each molecule:

- Treated patients
- Duration of the treatment
- Number of administered cycles
- Cumulative Dose (CD)
- Dose Intensity (DI)
- Relative Dose Intensity (RDI)
- Patients with RDI≥80%
- Patients with delayed administration
- Patients with dose reduction
- Patients with delayed administration and dose reduction
- Raisons for delay and dose reduction
- Early discontinuation and reasons

Table 4 : Calculated variables related to treatment

Calculated variable	Formula
By patient	
Cumulative Dose received (mg/m²)	Total administered dose (mg/m²) per patient considering the totality of received cycles.
Cumulative Dose Intensity (mg/m²/week)	Cumulative Dose received / Treatment duration (weeks)
Relative Dose Intensity (RDI)	Cumulative Dose Intensity / Dose Intensity planned in the protocol

Theoritical dose are as following:
Arm A-Gemcitabine each week, during 3 weeks then 1 week rest => 24 weeks:
- Gemcitabine: 1000 mg/m² per os,

Arm B–mFolfirinox every 2 weeks – 12 cycles => 24 weeks:
- Oxaliplatin: 85 mg/m²
- Irinotecan: 180 mg/m² => Reduce to 150 mg/m² after amendment
- Folinic Acid: 400 mg/m² (racemic) or 200 mg/m² (L-folinic acid)
- 5-FU: 2400 mg/m²

5.2.5 Safety evaluation

5.2.5.1 Adverse events

All treatment-relative adverse events (AE) will be described by toxicity category (SOC, System Organ Class). Severity of the AE's will be graded according to the NCI-CTCAE scale (version 4.0).

AEs will be described by patient.
The number of patients who underwent at least one AE will be described.
Every AE will be described according to the following categories:
- 6 grades (0,1,2,3,4,5),
- 0/1/2 vs 3/4/5.

Analysis by patient: If an AE is reported more than once during the treatment, the most severe grade will be reported for that given patient.

5.2.6 Primary and secondary endpoints assessment:

5.2.6.1 Primary endpoint: Disease Free Survival

The primary criterion defined in section 2.1 (DFS) will be analyzed using the methods described in section 5.3.2.

5.2.6.2 Secondary endpoints

Secondary endpoints OS, SS, and MFS defined in subsection 2.2 (survival data) will be analyzed according to the methods described in paragraph 5.3.2.

Secondary endpoint of tolerance defined in subsection 2.2 (qualitative criteria) will be analyzed according to the methods described in paragraph 5.3.1.2.

5.2.7 Concomitant treatments

Concomitant treatments will be listed in an appendix.

5.2.8 Relapse treatment

The first relapse treatment administered after the first progression (disease local and/or metastatic recurrence) will be described.

5.3 STATISTICAL PRINCIPLES

The analyses will be performed by treatment arm and overall.

All statistical tests are two sided and the significance threshold is set at 5% (i.e. $p<0.05$).

Statistical analyses will be performed using the STATA version 16.0 statistical software and a statistical report will be provided according to the current template.

5.3.1 Descriptive statistics

5.3.1.1 Continuous variables

Continuous variables will be described by the number of observations (N), the median, the minimum, the maximum. The Student T-test, Kruskal-Wallis or Wilcoxon test will be used to compare the distribution of continuous variables.

The normality will be checked using Kolmogorov-Smirnov test.

5.3.1.2 Categorical variables

Categorical variables will be described by the number of observations (N) and the frequency (%) of each modality. The missing categories will be counted.

Percentages will be calculated over the total population excluding missing data.

The Chi-square test will be used to compare proportions (or the Fisher's exact test if the expected frequencies are less than 5).

5.3.2 Time-to event data

Median follow-up will be estimated using reverse Kaplan-Meier method and is defined as the time from the date of randomization of the treatment to the date of last follow-up, death being censored.

The Kaplan-Meier method will be used to estimate survival rates and median survival times and their associated 95% confidence interval (95%CI). Survival curves will be presented.

The comparison of survival distribution between treatment arms will be performed using the Log-rank test.

Treatment and prognostic factors effects will be presented using hazard ratio with 95%CI.

Hazard Ratios (HR) with 95%CI will be estimated using a Cox proportional hazard model (stratified according stratification factors for treatment effect). The proportional-hazards assumption will be verified by the Schoenfel residual method for covariates.

5.3.3 Prognostic factors of DFS and OS

5.3.3.1 Univariate analysis

Variables that will be studied in the univariate analysis by the Log-rank test are presented in the following table.

Tableau 5 : Prognostic Factors

Prognostic factor	Coding
Arm	
Centre	≥10 patients / <10 patients
Gender	Male/Female
Age	<70 years / ≥ 70 years <75 years / ≥ 75 years
ECOG	
Diabete	No/Yes
Tumor location	Head/Other
Histotype	Ductal adenocarcinoma / Other
Tumor grading	Well / moderately / poorly differentiated
pT	T1-2 / T3-4
N	N- / N+
Tumor staging	
Lymph nodes ratio	Number of regional lymph nodes Invaded/retrieved 0 /]0-0.20] /]0.20-0.40] / >0.40
Number of regional lymph nodes retrieved	<12 / ≥ 12
Excision procedure	DPC / distal pancreatectomy / Total pancreatectomy
Resection	R0 / R1
Venous resection	Yes/no
Resection of superior mesenteric vein	Yes/no
Resection of portal vein	Yes/no
Sampling of paraaortic nodes	Yes/no
Embols	Yes/no
CA19.9 post surgery	≤90 / 91-180
Amendment	Before (Dose IRI=180mg/m²) vs After (dose

	IRI=150mg/m²)
Time between surgery – 1st dose of chemotherapy	≤ 8 weeks / > 8 weeks

5.3.3.2 Multivariate analyses

Variables with p-value <0.2 (at univariate analysis) or clinically relevant will be selected for multivariate analyses.

A Cox proportional hazard model using forward, backward or stepwise covariate selection techniques will be used.

Hazard ratios (HR) will be presented with their 95%CI. Treatment by covariate interactions will be explored. If significant interactions are detected a subgroup analysis will be performed.

5.3.3.3 Planned subgroup analyses

The heterogeneity of treatment effect on DFS and OS into subgroups will be assessed by interaction tests. The subgroups are prognostic factors listed in table 5.

A forest plot will be presented.

5.3.4 Missing data

Unless otherwise stated, missing values will not be imputed. If the day of a date is missing:
- it will be replaced by 1 for dates involved in survival analyses (relapse, death …)
- it will be replaced by 15 for all other dates (cf. macro: « date_extrapol_j15.ado»).

5.3.5 Additional analyses

- After an amendment the dose of Irinotecan was decreased from 180mg/m² to 150 mg/m² (from patient n°163) due to diarrhea. The prognostic effect on DFS of this dose reduction will be tested.

- Exploratory analysis to identify risk factors for the occurrence of diarrhea will be performed with the use of a logistic –regression model.

- To see the prognostic effect on overall survival of factors collected at the end of treatment (cf. table 6), a landmark method will be used. Any patient lost to follow-up or who died within 8 months of randomization will not be selected to avoid the potential bias as a result of treatment related death. We select an 8-month landmark point as Valle and al (ESPAC3, JCO 2014).

Tableau 6 : Prognostic Factors collected at the end of treatment

Prognostic factor	Coding
Full treatment	RDI for all drugs ≥ 80% Yes/no
Completion of chemotherapy	12 cycles for FOLFIRINOX or 6 cycles of Gemcitabine Yes/no FOLFIRINOX : 1 cycle=At least 5FU received
Treatment duration	<6 months / ≥6 months

- Treatment administration for the first 3 months will be compared between arms

- Time between first relapse and relapse treatment will be compared between the inclusion capacity of centers

- Impact of the time from end of chemotherapy to relapse on Overall Survival from relapse (OSr).
  For this analysis we will select the treated patients who had a local or metastatic relapse after the end of treatment.
  Any patients who progressed during treatment or who had a second cancer or death as first event will not be selected.

  OSr is defined as the interval between first relapse and the occurrence of death whatever the cause. Patients alive at the time of the analysis will be censored on the date of the last informative follow-up.
  Hazard Ratios (HR) with 95%CI will be estimated using a Cox proportional hazard model

  We will explore the impact of the time from end of chemotherapy to relapse on OSr as a continuous variable (HR estimated for a change of one month) and as a categorical variable using a 6-months and a 12-months cutoff.
  We will look for the optimal cut point to dichotomize the time from end of chemotherapy to relapse using the maximally selected Log rank statistics (package R maxstat).
- The number of metastasis sites and the localization of metastasis as first event will be compared between arms

- The median time and his 95%CI from randomization to first recurrence or to first distant recurrence will be presented according the localization

- The median Overall survival from first recurrence (OSr) will be presented according the localization of recurrence.

- The first relapse diagnosis method for loco regional and metastasis will be compared between arms.

6. APPENDICES

6.1 APPENDIX 1: LIST OF TABLES AND DATA LISTINGS

6.1.1 Baseline

N°	Title	Described parameters	Format*
1.0	Participating centres	Centres	*T*
2.0	Analysis populations	ITT, ITT modified, Safety population	*T+DI*
3.0	Randomisation	Stratification factors	*T*
4.0	Baseline characteristics	Gender, ECOG, BMI	*T*
5.0	Baseline characteristics	Age, usual weight, weight, height, body surface area, BMI,	*T*
6.0	Baseline araclinic exams	ECG	*T*
7.0	Surgery	Time, excision procedure, resection, etc	*T+DI*
8.0	Pathologic report	Tumor location, Histotype, tumor grade, etc.	*T+DI*
9.0	Tumor staging	pTNM	*T+DI*
10.0	Biological tests	Blood, ionogram, etc	*T+DI*
11.0	Comorbidities	Diabetes, tobacco use, chronic pancreatitis, HBP	*T+DI*

T= Table
DI= Data listing

6.1.2 Treatment Administration

N°	Title	Described parameters	Format*
12.0	Chemotherapy administration	Patients treated, duration of treatment, number of administrations Cumulate dose, Dose Intensity (DI), Relative Dose Intensity (RDI), Patients with a RDI≥80%	*T*
13.0	Delay and modification of dose level	Patients with administration delayed, Patients with dose reduction, Delay and dose reduction, Reasons of delay and dose reduction, Early stop and reason	*T+DI*

6.1.3 Safety evaluation

N°	Title	Described parameters	Format*
14.0	Toxicity by patient	Maximal grade for all toxicities	*T*
15.0	Toxicity by patient	Maximal Grade by SOC	*T*
16.0 à 16.XX	Toxicity by patient		*T*

6.1.4 Efficacy

N°	Title	Described parameters	Format*
17.0	Primary endoint	DFS	*T*
18.0	Secondary endpoints	OS, Specific Survival, Metastasis free survival	*T*
19.0	Cause of deaths	Vital status, Cause of death	*T + DI*
20.0	Carcinologic events	Nature of relapse, diagnostic of relapse	*T + DI*

6.1.5 Relapse treatment

N°	Title	Described parameters	Format*
21.0	Relapse treatment	Surgery: Operated patients Radiotherapy: Treated patients Chemotherapy: Treated patients	*T+DI*

6.1.6 Prognostic factors of DFS and OS

N°	Title	Described parameters	Format*
22.0	Prognostic factors of DFS	Univariate analysis	*T*
23.0	Prognostic factors of DFS	Multivariate analysis	*T*
24.0	Prognostic factors of OS	Univariate analysis	*T*
25.0	Prognostic factors of OS	Multivariate analysis	*T*