Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011;364:1817-25.

PAC ACCORD
Concerted Actions in Colorectal and Digestive Tract Cancers

[French title: **A**ctions concertées dans les **C**ancers **CO**lo**R**ectaux et **D**igestifs]

ACCORD PROTOCOL 11/0402

EudraCT No. 2004-001985-42

RANDOMIZED PHASE II/III TRIAL COMPARING Folfirinox (OXALIPLATIN/IRINOTECAN/LV5FU) WITH GEMCITABINE IN FIRST-LINE CHEMOTHERAPY OF PATIENTS WITH METASTATIC PANCREATIC CANCER

OXIPAN Trial

Version 9, containing amendments 1, 2, 3, 5, 7, 8, 9 and 10, approved by CPP EST-III May 7, 2009

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APPROVAL AND SIGNATORIES
TO ACCORD PROTOCOL 11/0402 CONTAINING
AMENDMENTS 1, 2, 3, 5, 7, 8, 9 and 10

EudraCT No. 2004-001985-42

RANDOMIZED PHASE II/III TRIAL COMPARING Folfirinox (OXALIPLATIN/IRINOTECAN/LV5FU) WITH GEMCITABINE IN FIRST-LINE CHEMOTHERAPY OF PATIENTS WITH METASTATIC PANCREATIC CANCER

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I acknowledge that I have read the entire ACCORD 11/0402 protocol, and undertake to conduct this protocol in accordance with Good Clinical Practice, the Huriet Act and as described in this document.

I hereby assume the responsibilities incumbent upon me as principal investigator, including the following:

- Collection of the informed consent, dated and signed, prior to any selection procedure in the protocol,
- Validation of completed observation notebooks for each patient included in the study,
- Direct access to source documents for verification by the clinical research associate (CRA) appointed by the sponsor,
- Archiving of essential study documents for 15 years.

PRINCIPAL INVESTIGATOR OF THE ESTABLISHMENT CONCERNED:

Name and address of establishment:

Name of principal investigator:

Date: Signature:

ACCORD PROTOCOL 11/0402 SYNOPSIS

SPONSOR	Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) [National Federation of Cancer Centers]
COORDINATOR	Prof. Thierry CONROY Department of Oncology, Centre Alexis Vautrin 6, avenue de Bourgogne 54511 Vandœuvre-lès-Nancy Cedex
TITLE	Randomized Phase II/III trial comparing Folfirinox (oxaliplatin/irinotecan/LV5FU) with gemcitabine in first-line chemotherapy of patients with metastatic pancreatic cancer
PATHOLOGY	Metastatic pancreatic adenocarcinomas
OBJECTIVES	**Main objective of Phase II:** ▪ Compare objective response rates between the 2 treatment arms. **Main objective of Phase III:** ▪ Compare survival. **Secondary objective of Phase II:** ▪ Compare the toxicity of these treatments. **Secondary objectives of Phase III:** ▪ Compare progression-free survival in the 2 arms. ▪ Compare quality of life in the 2 arms. ▪ Compare response rates. ▪ Compare the toxicity of these treatments.
METHODOLOGY	Randomized Phase II/III trial comparing Folfirinox (oxaliplatin/irinotecan/LV5FU) with gemcitabine in first-line chemotherapy for patients with metastatic pancreatic cancer.
INCLUSION CRITERIA	▪ Histologically or cytologically proven adenocarcinoma of the pancreas, ▪ Metastatic disease, ▪ Measurable disease outside an irradiated area, ▪ A lesion is measurable if it can be accurately measured in at least one dimension (the largest diameter being reported) either >20 mm with a conventional scanner, or >10 mm with a spiral scanner. ▪ No previous chemotherapy, ▪ No previous abdominal radiotherapy (with the exception analgesic radiotherapy if not performed on measurable targets), ▪ Age between 18 and 75 inclusive, ▪ General condition: WHO 0-1, ▪ Satisfactory hematological function (PNN $\geq$1500/mm^3, platelets $\geq$100,000/mm^3), ▪ Satisfactory liver function (bilirubin ≤1.5 times the upper limit of normal (biliary drainage is permitted)), ▪ Satisfactory renal function: creatinine <120 µmol/L, i.e. 13.6 mg/L, ▪ Absence of heart failure or non-medically controlled angina pectoris or infarction in the 12 months prior to inclusion, ▪ Informing the patient and signature of the informed consent form.

<table>
<tr><td>NON-INCLUSION CRITERIA</td><td>
▪ Other types of pancreatic tumors, in particular endocrine or acinar cell tumors,
▪ Presence of brain or meningeal metastases,
▪ Contraindications specific to the treatment studied,
▪ History of chronic diarrhea or inflammatory disease of the colon or rectum, or of occlusion or sub-occlusion unresolved by symptomatic treatment,
▪ Active progressive infection or other serious underlying pathology likely to prevent the patient from receiving treatment,
▪ Other concomitant cancer or history of cancer other than cancer in situ of the uterine cervix or basal or squamous cell carcinoma,
▪ Patient already included in another therapeutic trial with an experimental compound,
▪ Women who are pregnant, may become pregnant or are breast-feeding,
▪ Persons deprived of their liberty or under guardianship,
▪ Inability to undergo medical follow-up for geographical, social or psychological reasons.
</td></tr>
<tr><td>BRIEF DESCRIPTION OF PRODUCTS AND TREATMENT PROCESS</td><td>
Arm A: Folfirinox

- Oxaliplatin 85 mg/m^2 IV infusion over 2 hours
- Irinotecan 180 mg/m^2 IV infusion over 90 min.
- Folinic acid 400 mg/m^2 IV 2-hour infusion
- 5-FU bolus 400 mg/m^2 IV over 5 minutes
- Continuous 5-FU 2.4 g/m^2 IV infused over 46 hours.
Cycle restart at D15.

Arm B: gemcitabine

- Gemcitabine 1,000 mg/m^2 at D1, D8, D15, D22, D29, D36, D43.
Resumption at D57 and continuation of treatment for 3 weeks out of 4.
</td></tr>
<tr><td>EVALUATION ENDPOINT</td><td>
For Phase II
Efficiency
Primary endpoint: objective response rate (RECIST).
Secondary endpoint: grade 3-4 toxicities.

For Phase III

Primary endpoint: survival
Secondary endpoint: Quality of life (EORTC QLQ-C30 score, version 3.0, every 14 days).
Toxicities according to NCI-CTC scale version 3.0.
Progression-free survival, response rate.
</td></tr>
<tr><td>NUMBER OF PATIENTS REQUIRED</td><td>
For Phase II:

Patients will be enrolled in 3 staging points, with an assessment of the response rate in Arm A (Folfirinox) at each stage.

<table>
<tr><td>Staging points</td><td>1st</td><td>2nd</td><td>3rd</td></tr>
<tr><td></td><td></td><td></td><td></td></tr>
<tr><td>N</td><td>20</td><td>30</td><td>40</td></tr>
<tr><td>R</td><td>2</td><td>4</td><td>6</td></tr>
<tr><td>A</td><td>8</td><td>11</td><td>–</td></tr>
</table>
N = Number of patients planned in Arm A Folfirinox
R = Number of patients responding to Folfirinox
A = Number of responding patients, beyond which Phase II is discontinued. Folfirinox is then considered to have produced at least 20% objective responses, and Phase III is initiated.

♦ At the end of the first stage (20 patients included):
- If 2 or fewer objective responses (ORs) are observed,
</td></tr>
</table>

	the trial is stopped, with the conclusion that Folfirinox is not effective. - If 8 or more objective responses are observed, Phase III is initiated. - If between 3 and 7 objective responses are observed, Phase II is initiated: inclusion of 10 additional patients. ♦ At the end of the second stage (30 patients in all): - If 4 or fewer objective responses are observed, it is concluded that Folfirinox is not effective. - If 11 or more objective responses are observed, it is concluded that Folfirinox is effective, and Phase III is initiated. - If between 5 and 10 objective responses are observed, Phase II is initiated: inclusion of 10 additional patients. ♦ At the end of the third stage (40 patients in all): - If 6 or fewer objective responses are observed, it is concluded that Folfirinox is not sufficiently effective, and Phase III is not initiated. - If 12 or more objective responses are observed, it is concluded that the treatment is effective, and Phase III is initiated. - Between 7 and 11, no conclusions can be drawn, and Phase III is initiated to acquire more patients. Given that 10% of patients will be unassessable, for response it is therefore necessary to include a **total of 88 patients** divided into **2** equivalent **groups of 44 patients** over a 2-year period. **For Phase III:** To demonstrate a difference in median survival of 3 months (from 7 to 10 months median), i.e. a relative risk of 0.70, **360 patients** would have to be included to maintain an overall alpha risk of 5%, accepting a beta risk of 20% (trial power=80%). This power will be obtained when **250** events have been observed (calculated using East 5 software). Patients included in Phase II will be included in the Phase III study.
ESTIMATED NUMBER OF CENTERS	15 centers for Phase II 50 centers for Phase III
DURATION OF STUDY	Start of Phase II inclusions: June 2004 End of Phase II inclusions: June 2006 Start of Phase III enrollment: June 2006 End of Phase III inclusions: June 2009 End of study: June 2010
STATISTICAL ANALYSIS	Statistical analysis will be performed on all patients randomized on an intention-to-treat basis. Overall survival of eligible patients will be calculated from the date of randomization; progression-free survival (PFS) will be calculated from the date of randomization to the date of relapse; progression-free survival rates will be estimated using the Kaplan-Meier technique; and comparisons will be made using a log-rank test. A Cox model will be used for multifactorial analysis, taking into account the major prognostic factors for survival in metastatic disease (general state of health, and, more secondarily, age, tumor differentiation, albuminemia, LDH, and alkaline phosphatases).

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1. INTRODUCTION AND RATIONALE OF THE TRIAL

1.1 Should metastatic exocrine pancreatic cancer be treated with chemotherapy?

Metastatic pancreatic cancer remains an incurable disease, associated with a median survival of 2-4 months in the absence of chemotherapy (1-2). Seven studies have compared palliative chemotherapy with purely symptomatic treatment (3-9). Four studies dating from the 1980s showed no difference in survival between the two groups (3-6). Two of the three most recent studies showed an improvement in survival and quality of life in favor of the chemotherapy group (7,8). In the first study (7), chemotherapy-treated patients were less depressed (HADS scale). In the second study (8), 38% of patients treated with chemotherapy improved their quality of life (judged by two independent observers on the basis of responses to the EORTC QLQ-C30 questionnaire) for more than four months, compared with 13% of patients receiving symptomatic treatment. The chemotherapy group had a better Karnofsky index, better psychological status, and less anorexia, pain, fatigue, and dyspnea.

However, the few open studies that have investigated the impact on symptom regression and quality of life indicate that at best 20-35% of patients benefit from chemotherapy, with the benefit usually being short-lived (10). In multifactorial analysis, the prognostic factors for survival in metastatic disease are mainly general condition, with secondary factors being age, tumor differentiation, anorexia, albumin levels, LDH, and alkaline phosphatases (11-15-19-47-51). A study of 3,023 patients treated with gemcitabine also showed a particularly short median survival in patients with a Karnofsky index below 70 (schematically equivalent to WHO 2), with a median survival of 2.4 months, and progression-free survival of 1.7 months (11). The decision to treat WHO 2 patients must therefore be taken on a case-by-case basis.

1.2 Gemcitabine is the reference chemotherapy

Following a randomized trial involving 126 patients (12), gemcitabine 1,000 mg/m^2 administered weekly is considered the reference monochemotherapy. It was marginally more effective than 5-FU administered as a bolus 5 days every four weeks. However, with gemcitabine, only three partial responses were observed among 56 patients with measurable disease (5.4%), whereas none of the patients treated with 5-FU responded. Median survival was improved by 1.2 months, from 4.4 months for patients treated with 5-FU versus 5.6 months for patients receiving gemcitabine ($p = 0.0025$). In other randomized studies, gemcitabine monotherapy was associated with a median survival of 4.4 to 6.6 months (13-17). No randomized study to date has shown a significant improvement in survival and/or quality of life compared with gemcitabine monotherapy (17-40-41-42-44-46-47- 48-49). Gemcitabine is currently the reference treatment in most randomized studies (EORTC, FFCD, American cooperative groups).

1.3 Results obtained with 5-FU, irinotecan, and oxaliplatin

The historical response rate attributed to 5-Fluorouracil (15% to 36%) is highly overestimated, as shown by 3 recent randomized studies. In a study of 281 patients, continuous infusion of 5-FU at a dose of 225 mg/m^2/d produced a response rate of just 1% and a median survival of 5.1 months (18). At a dose of 300 mg/m^2/d, the response rate observed in 105 patients was 8.6%, with a median survival of 5.1 months (19). In the FNCLCC study, the response rate for bolus 5-FU was 0% versus 12% for a combination of continuous infusion 5-FU and cisplatin (20), with no significant survival advantage for the combination.

Irinotecan is an active drug in pancreatic cancer, associated with response rates of 6-9%, responses lasting a median of 5.7 months, with a median survival of 5.2 months (21-22). Third- or fourth-line efficacy has also been described (45). Oxaliplatin as a monotherapy

is not effective, but combined with 5-fluorouracil and folinic acid, a 12% response rate was reported in 28 patients. Median survival was 8.5 months (23). In vitro synergy between SN-38, the active metabolite of Irinotecan, and oxaliplatin has been described (24).

SN-38, the main metabolite of irinotecan, is more cytotoxic on pancreatic adenocarcinoma cultures than cisplatin, mitomycin C and 5-FU (31). Other pre-clinical studies have shown synergy between SN-38 and 5-FU when SN-38 precedes exposure to 5-FU (32). Other laboratory studies have confirmed the antitumor effect of irinotecan on pancreatic tumor cell cultures and on pancreatic cancer xenografts (34).

The cytotoxic effect of oxaliplatin has been described on three different pancreatic cell lines and on liver metastases of pancreatic cancer (29). In vitro, cytotoxicity is enhanced when oxaliplatin is added to cultures before or at the same time as a camptothecin derivative (35). This synergy appears to be linked to the stabilization of oxaliplatin adducts on DNA when tumor cells are exposed first to oxaliplatin, then to the topoisomerase inhibitor. Irinotecan could therefore reduce resistance to oxaliplatin. Apart from hematological toxicity, these two drugs have no cross-toxicity. In the Phase I study of the Folfirinox combination (oxaliplatin, irinotecan, folinic acid, 5-FU bolus, 5-FU continuous infusion), complete and partial responses were observed in five cases of pancreatic cancer (25).

1.4 Results of the Folfirinox Phase II study

Given the encouraging results observed in Phase I, a Phase II trial of the Folfirinox combination was set up in 9 centers. Forty-seven WHO 0-1 patients with locally advanced or metastatic disease were included. Forty-six patients were treated. Thirty-four patients had metastatic disease and 12 had inoperable locally advanced disease. The mean number of courses was 8 (1-24). Tolerance was excellent. Out of 356 cycles, 14% were dose-reduced. Four patients received G-CSF. Two episodes of febrile neutropenia occurred. Thirty-five percent of patients experienced grade 3 neutropenia (15% of cycles) and 17% grade 4 neutropenia (7% of cycles). Grade 3 diarrhea occurred in 11 patients and 3% of cycles. Grade 4 diarrhea occurred in 2% of patients and less than 1% of cycles. Oxaliplatin neurotoxicity was tolerable, with grade 3 neuropathy (Levi scale) occurring in 15% of patients and 3% of cycles. There were no toxic deaths.

In terms of response rates, after independent external review of all scans, there were two complete responses, ten partial responses, twenty tumor stabilizations, representing a response rate of 26% (confidence interval: 13-39%), and 61% tumor control. The response rate was identical in metastatic and locally advanced disease.

Progression was observed within an average of 5.1 months. Median survival was 10.2 months (9.5 months in metastatic disease and 15.5 months in locally advanced cancers). Forty-three percent of patients were alive at one year. The mean duration of objective response was 9.3 months (8-14 months) and the mean duration of stability was 6.2 months (26-27).

Quality of life was assessed at inclusion and before each cycle. Compliance with the questionnaire was 66%. Thirty-eight questionnaires were available at inclusion and 36 at the last cycle. Comparison of initial quality-of-life scores with those of the last cycle showed an improvement in all domains of the QLQ-C30 (except cognitive domain, financial difficulties and diarrhea). The improvement is most marked in responders or stable patients. Scores improved by more than 10 points in the activity, psychological and social domains, while symptom scores were reduced, especially for pain, insomnia, loss of appetite and constipation. In responders, the improvement in overall quality of life averaged 25 points on a scale of 100 (i.e., a “major” improvement

according to OSOBA criteria (28)). These encouraging results justify a randomized study of Folfirinox versus the reference treatment, gemcitabine monotherapy.

2. OBJECTIVES OF THE TRIAL

2.1 Main objective of Phase II

To evaluate the efficacy of the combination of oxaliplatin, irinotecan, 5-fluorouracil, and folinic acid (Folfirinox, Arm A) in the treatment of metastatic pancreatic cancer compared with the reference treatment of gemcitabine (Arm B), by comparing objective response rates between the 2 arms.

2.2 Secondary objectives of Phase II

- Compare treatment tolerance, particularly grade 3-4 toxicities.

2.3 Main objective of Phase III

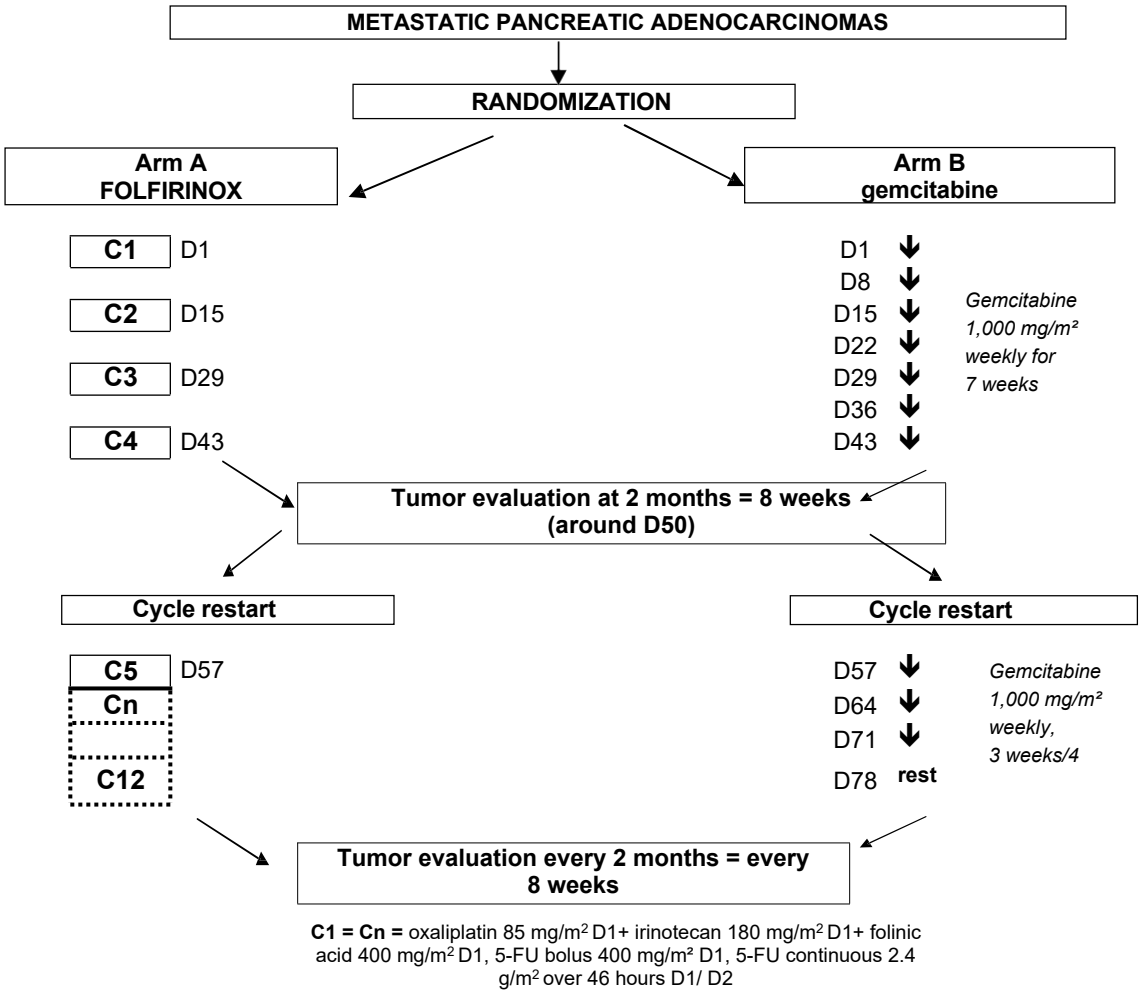
The main objective is to compare the effects on overall survival of two treatment regimens, the Folfirinox, Arm A combination versus the reference treatment with gemcitabine, Arm B.

2.4 Secondary objectives of Phase III

- Compare progression-free survival in the 2 arms
- Compare quality of life in the 2 arms
- Compare response rates
- Compare toxicity with treatments

3. METHODOLOGY

Randomized, open-label, multicenter, Phase II/III Direct Individual Benefit (DIB) trial comparing treatment A (Folfirinox) with treatment B (gemcitabine).



Patients will be treated for a recommended maximum of 6 months.

4 PATIENT SELECTION

4.1 Inclusion criteria

1. Histologically or cytologically proven adenocarcinoma of the pancreas,
2. Metastatic disease,
3. Disease measurable outside an irradiated area

   A lesion is measurable if it can be accurately measured in at least one dimension (the largest diameter being reported) either >20 mm with a conventional scanner, or >10 mm with a spiral scanner.
4. No previous chemotherapy,
5. Absence of previous abdominal radiotherapy (with the exception of analgesic radiotherapy if not performed on measurable targets),
6. Age between 18 and 75 inclusive,
7. General condition: WHO 0-1,
8. Satisfactory hematological function (PNN $\geq$ 1,500/mm^3, platelets $\geq$ 100,000/mm^3),
9. Satisfactory liver function (bilirubin ≤1.5 times the upper limit of normal (biliary drainage is permitted)),

10. Satisfactory renal function: creatinine <120 µmol/L, i.e. 13.6 mg/L,
11. Absence of heart failure or non-medically controlled angina pectoris or infarction in the 12 months prior to inclusion,
12. Patient information and signature of informed consent.

4.2 Non-inclusion criteria

1. Other types of pancreatic tumors, in particular endocrine or acinar cell tumors,
2. Presence of brain or meningeal metastases,
3. Contraindications specific to the treatment studied,
4. History of chronic diarrhea or inflammatory disease of the colon or rectum, or of occlusion or sub-occlusion unresolved by symptomatic treatment,
5. Active progressive infection or other serious underlying pathology likely to prevent the patient from receiving treatment,
6. Other concomitant cancer or history of cancer other than cancer in situ of the uterine cervix or basal or squamous cell carcinoma,
7. Patient already included in another therapeutic trial with an experimental molecule,
8. Women who are pregnant, may become pregnant or are breast-feeding,
9. Persons deprived of their liberty or under guardianship,
10. Inability to undergo medical follow-up for geographical, social or psychological reasons.

5. RANDOMIZATION/PATIENT REGISTRATION

After signing the consent form and validating the results of the initial inclusion assessment, eligible patients will be randomized at the trial's randomization center.
The investigator must fax the completed and signed randomization form to EURAXI Pharma's Data Management Center, Biometrics Department. In return, the Data Management Center will fax confirmation of randomization, specifying the treatment arm and patient number.

The coordinates of the randomization center are:

Randomization and Data Management

Sébastien LOUVEAU
EURAXI PHARMA
Biometrics Department

Monday to Friday, 9 a.m. to 4 p.m.
Fax: 02.47.74.30.82 / Telephone: 02.47.74.30.47

The random sampling is stratified classically based on:

- **The center**
- **WHO general condition (0 versus 1)**
- **Location (head versus other)**

Treatment must begin within 7 days of randomization.

6. TREATMENTS

6.1 Description of trial treatments

After random selection, subjects receive either treatment A (Folfirinox) or treatment B (gemcitabine):

Treatment A: Folfirinox

- Oxaliplatin (Eloxatine®) 85 mg/m² D1 in 2h, subsequently
- Irinotecan (Campto®) 180 mg/m² D1 in 90 min.
- Folinic acid 400 mg/m², D1 in 2h (during irinotecan infusion)
- 5-FU bolus 400 mg/m² D1 followed by continuous 5-FU 2.4 g/m² **in total** over 46 hours, **i.e. 1.2 g/m² on D1 and 1.2 g/m² on D2.**

Treatment should be continued until progression, and a maximum of 12 cycles is recommended.

Folinic acid can be replaced by calcium levofolinate for centers wishing to do so. The dose then becomes 200 mg/m².

Treatment B: gemcitabine

- Gemcitabine 1,000 mg/m² over 30 min by strict intravenous route, on D1, D8, D15, D22, D29, D36, D43.

Resumption of gemcitabine at D57, 3 weeks out of 4 (D57, D64, D71 followed by a one-week break).

Treatment with gemcitabine should be continued according to the same schedule (3 weeks out of 4) until progression, and a maximum of 6 months is recommended.

Products will be prepared in accordance with Good Chemotherapy Practice, as described in Annex 1.

Irinotecan and oxaliplatin will be supplied by the sponsor. Other products will be taken from the pharmacy's usual stock.

Oxaliplatin and irinotecan will be supplied by the sponsor:

→ These products will be labeled in compliance with article R.5123 of the French Public Health Code and with the Recommendations of Annex 1 of the European Good Manufacturing Practices.

→ These products will be distributed to the various pharmacies in the care facilities in accordance with Good Distribution Practices (GDP).

Traceability of all products used in this clinical study, which are supplied either by the sponsor or by the pharmacy of the care facility, must be ensured throughout the duration of the study.

6.2 Treatment sequence

6.2.1 Arm A: Folfirinox: combination of oxaliplatin+irinotecan+folinic acid+5-fluorouracil

Treatment will begin with oxaliplatin 85 mg/m^2 IV infused over 2 hours, followed by folinic acid 400 mg/m^2 IV infused over 2 hours and irinotecan 180 mg/m^2 IV infused over 1.5 hours, to be started immediately after completion of the oxaliplatin infusion.
5-FU will be administered immediately after completion of the folinic acid infusion and will consist of a 5-minute IV bolus dose of 400 mg/m^2, followed by a 46-hour continuous infusion of 2.4 g/m^2.

The cycle is administered every 2 weeks. Treatment can be carried out in a day hospital.

Treatment should be continued until relapse, and a maximum of 12 courses is recommended.

6.2.2 Arm B: gemcitabine

Gemcitabine is administered at a dose of 1,000mg/m^2 over 30 minutes by strict intravenous injection.

Administration should be repeated **once a week for 7 weeks, followed by a 14-day rest.** Then, starting with the next cycle, administration should be repeated once a week for **3 consecutive weeks, followed by a week's rest.** Doses may be reduced prior to each chemotherapy administration, depending on patients' individual tolerance to gemcitabine.

6.2.3 Duration of treatment (for both arms)

6 months of chemotherapy are recommended. Beyond this protocol treatment period, the investigator is free to decide whether or not to treat the patient with medication.

Similarly, in the event of progression, the therapeutic management of the patient is at the discretion of the investigator.

6.3 Dose adjustment

If dose reduction is necessary, the reduced dosage should be maintained thereafter. Any recurrence of Grade 4 toxicity despite dose reduction will prompt the patient to discontinue treatment.

PATIENTS NEVER EXIT THE STUDY.
THEY ARE FOLLOWED UP UNTIL DEATH.

6.3.1 Hematological toxicity

6.3.1.1 According to biological results at D15

TREATMENT A: Folfirinox

CBC at D15	CYCLE DELAY	DOSE REDUCTION		
		Irinotecan (CPT-11)	**Oxaliplatin (L-OHP)**	**LV5FU**
PNN ≥1.5 x 10^9/L and platelets ≥75 x 10^9/L	No cycle delay	No dose reduction		
PNN <1.5 x 10^9/L	Delay treatment until PNN 1,500 (until D22 or D29 if necessary). If no recovery at D29, **discontinuation of treatment***	1st episode: dose reduction to 150 mg/m² 2nd episode: dose maintained at 150 mg/m² 3rd episode: **discontinuation of treatment**	1st episode: no dose reduction 2nd episode: reduce dose to 60 mg/m² 3rd episode: **discontinuation of treatment**	1st episode: eliminate bolus on D1
Platelets <75 x 10^9/L	Delay treatment until recovery (platelets ≥75 x 10^9/L) If no recovery at D29, **discontinuation of treatment**	1st episode: no dose reduction 2nd episode: reduce dose to 150 mg/m² 3rd episode: **discontinuation of treatment**	1st episode: reduce dose to 60 mg/m² 2nd episode: maintenance of reduced dose 3rd episode: **discontinuation of treatment**	1st episode: reduce bolus and continuous infusion dose by 25%

* *If there is no recovery after 2 treatment delays, discontinue treatment unless there is a clear clinical benefit: the case will then be discussed with the study coordinator and the sponsor.*

TREATMENT B: gemcitabine

CBC before each administration	CYCLE DELAY	DOSE REDUCTION
Granulocytes >1 x 10^9/L and platelets >100 x 10^9/L	No cycle delay	Administer 100% of total dose
0.5 < Granulocytes ≤ 1 x 10^9/L **or** 50 < platelets ≤ 100 x 10^9/L	No cycle delay	Administer 75% of total dose (25% dose reduction)
Granulocytes ≤ 0.5 x 10^9/L **or** platelets ≤ 50 x 10^9/L	Delay treatment until recovery of 500 granulocytes and 50,000 platelets.	No dose reduction

6.3.1.2 According to intercure hematological toxicity (nadir) in the Folfirinox arm

EVENTS	DOSE REDUCTION IN NEXT CYCLE
- Isolated febrile neutropenia - Neutropenia G4 lasting more than 7 days - Infection with concomitant grade 3-4 neutropenia	1st episode: reduce CPT-11 dose to 150 mg/m^2 and eliminate 5-FU bolus at D1 2nd episode: despite CPT-11 dose reduction and 5-FU bolus elimination, reduce L-OHP dose to 60 mg/m^2 3rd episode: **discontinuation of treatment**
Grade 3-4 thrombocytopenia	1st episode: reduce L-OHP dose to 60 mg/m^2 and continuous 5-FU dose by 25% 2nd episode: despite dose reduction to 60 mg/m^2, reduce CPT-11 dose to 150 mg/m^2 and continuous 5-FU dose by a further 25% 3rd episode: **discontinuation of treatment**

6.3.2 Digestive toxicities in the Folfirinox arm

EVENTS	DOSE REDUCTION IN NEXT CYCLE
- Isolated grade **3-4** diarrhea or - Diarrhea+fever and/or grade 3-4 neutropenia	1st episode: reduce CPT-11 dose to 150 mg/m^2 and eliminate 5FU bolus at D1 2nd episode: despite CPT-11 dose reduction to 150 mg/m^2, reduce L-OHP dose to 60 mg/m^2 and reduce continuous 5FU dose by 25% 3rd episode: treatment discontinued
Resistant diarrhea (>48 h) despite high doses of loperamide	No dose reduction of CPT-11, L-OHP or 5-FU after recovery unless grade 3-4 diarrhea, or grade 3-4 diarrhea+fever and/or neutropenia.

6.3.3 Mucositis or hand-foot syndrome in the Folfirinox arm

These toxicities are caused by 5-FU.
In the event of grade 3-4 toxicity, the dosage of bolus 5-FU and continuous 5-FU is reduced by 25% for subsequent courses of treatment.

6.3.4 Cardiac toxicity

In the event of angina pectoris or myocardial infarction, treatment should be discontinued.

6.3.5 Peripheral neuropathy

To assess toxicity, patients must have received at least one course of treatment. As the modified specific scale of Lévi et al. (37) is not precise enough, neurological toxicity will be assessed using the NCI toxicity scale version 3.0 (Annex 5).

The neurological toxicity of oxaliplatin requires special attention, and it should be pointed out that its grading is complex using the NCI CTC criteria version 3.0. The various neurological toxicities can be classified as follows:

- Acro-dysesthesia to cold, without pain or dysesthesia (tingling, pins and needles): will be rated as “Neuropathy, Sensory”
- Objective motor disorders discovered by clinical or symptomatic examination: will be rated as “Neuropathy, Motor”
- Jaw pain, cramps, painful neuropathy: make sure to give an additional “Pain” score.

If oxaliplatin is discontinued due to neurotoxicity, irinotecan and 5-FU should be continued.

6.3.6 Dose adjustment for elevated bilirubin

If bilirubin levels rise, irinotecan dose adjustment is necessary.

EVENTS	DOSE REDUCTION IN NEXT CYCLE
35 < bilirubin ≤ 50 µmol/l	reduce CPT-11 dose to 75%.
bilirubin > 50 µmol/l	reduce CPT-11 dose to 50%.

6.3.7 Other toxicities

Any other ≥ grade 2 toxicity, except anemia and alopecia, may justify a dose reduction in each protocol if medically indicated:

- Treatment A Folfirinox: reduce CPT11 to 150 mg/m^2 and/or L-OHP to 60 mg/m^2 and/or 5-FU by 25% depending on the type of toxicity.
- Treatment B gemcitabine: 25% dose reduction.

6.4 Symptomatic treatment of toxicities

6.4.1 Cholinergic syndrome

In the event of acute cholinergic syndrome (hypersudation, hypersalivation, visual disturbances, lacrimation, miosis, abdominal cramps, diarrhea), a subcutaneous injection of 0.25 mg of atropine will be given as a remedial measure, then as a preventive measure in subsequent courses, unless contraindicated in patients treated with CPT-11.

6.4.2 Late-onset diarrhea

Prophylactic treatment:

No prophylactic treatment should be given, in particular loperamide should not be administered prophylactically. However, patients should discontinue laxative therapy and avoid foods and beverages known to accelerate intestinal transit.

Remedial treatment:

- At the first loose or liquid stool, the patient should immediately take 2 capsules of loperamide per os, then 1 capsule every 2 h for at least 12 h after the last loose stool, without exceeding a total treatment duration of 48 h. Patients should also be advised to take electrolyte-rich drinks throughout the diarrhea episode.

- If diarrhea persists for more than 48 hours despite the recommended treatment with loperamide, broad-spectrum antibiotic therapy (fluoroquinolone) should be initiated for a systematic period of 7 days, on medical advice.
- In the event of persistent and/or severe diarrhea, the patient will be hospitalized for parenteral rehydration, and loperamide will be replaced by another antidiarrheal treatment chosen by the investigating physician.
- Oral fluoroquinolone antibiotic therapy should also be prescribed in cases of grade 4 diarrhea or diarrhea associated with grade 3-4 neutropenia or fever.
- Patients with vomiting, fever or performance status >2 concomitant with diarrhea should be hospitalized promptly for parenteral support. Loperamide and fluoroquinolone should be prescribed as soon as the patient is discharged from hospital, so that both are available as soon as diarrhea appears.

6.4.3 Neutropenia

In the case of severe neutropenia, i.e. grade 3-4, patients are at high risk of febrile neutropenia and infection, particularly in the event of concomitant diarrhea. Should these symptoms appear, dosage adjustments are planned for the following cycle (see Section 6.3.2).

The administration of hematopoietic growth factors is not recommended in the first cycle, but may be indicated on a case-by-case basis depending on the patient's clinical condition. In such cases, treatment with filgrastim (Neupogen®) is recommended in accordance with the recommendations given in Annex 10.

In the event of anemia (e.g. hemoglobin level ≤11 g/dl), treatment with darbepoetin alfa (Aranesp®) should be initiated in accordance with the recommendations in Annex 11.

Aranesp® should not be administered if the hemoglobin level is >11 g/dL. It is necessary to ensure that this level does not exceed 13 g/dL. If hemoglobin levels rise by more than 2 g/dL in four weeks, reduce dosage by 25-50%.

6.4.4 Extravasation

Severe reactions linked to extravasation of irinotecan or oxaliplatin have been reported (36). General recommendations in the event of extravasation are as follows:
– Stop the infusion immediately,
– Do not remove needle or catheter,
– Use the same needle to aspirate as much of the infiltrated product as possible,
– Apply ice to the infiltrated area for 15 to 20 minutes every 4 to 6 hours for 72 hours,
– Local corticosteroid therapy,
– Check the infiltrated site regularly over the next few days, to see if any treatment is required. Do not hesitate to seek surgical advice if in doubt.

6.4.5 Nausea and vomiting

Prior to oxaliplatin administration, a combination of corticosteroids (30 min before) and anti 5HT3 (setron, 15 min. before) is recommended.

Prevention of delayed nausea and vomiting is also recommended, using metoclopramide (or a setron) and possibly corticosteroids.
WARNING: Corticosteroids should be used with extreme caution in diabetic patients.

6.4.6 Alopecia

Scalp-cooling caps are authorized, except in the case of cranial bone metastases.

6.5 Concurrent treatments

No anti-tumor treatment (chemotherapy, hormonal therapy, biological response modifiers) will be used.
All symptomatic treatments necessary for patient comfort (antiemetics, antidiarrheals) are authorized, along with their nature, dosage and duration of administration, as well as any other treatment justified by a medical indication.
Corticosteroids should not be used except in emergency situations or for antiemetic purposes. They should be used with the utmost caution in diabetic patients.
Radiotherapy for analgesic purposes is also permitted (irradiated bone marrow <20%). If the only measurable target were to be irradiated, the patient would stop treatment.

Associating warfarin (Coumadine®) with a Folfox protocol is not recommended (50). Heparin and its derivatives are preferable. If warfarin cannot be avoided, prothrombin levels should be checked more frequently and INR monitored.

Metronidazole and ornidazole increase 5-fluorouracil toxicity by reducing its clearance.

Risk of convulsion due to interaction between phenytoin and oxaliplatin. Phenytoin is therefore contraindicated.

7. INCLUSION AND FOLLOW-UP OF PATIENTS

Patient monitoring since the date of the random draw and the patient assessment schedule are described in Annex 2.

7.1 Inclusion report

Patients who are eligible for the trial and have signed their consent to take part must undergo an initial check-up **within 8 days** of the start of treatment, with the exception of paraclinical examinations, which may be carried out **within 3 weeks** of randomization.

- **Clinical examination**
  Clinical examination with determination of weight, height, and body surface area, ECOG performance index (Annex 3),
  Collection of concomitant treatments.
- **Paraclinical examination**
  Thoracic-abdominopelvic scan, ECG
- **Biological tests**
  Hematology and coagulation: CBC, platelets, PT, TCK
  Blood electrolytes, serum calcium
  Liver function tests (total, free, and conjugated bilirubin, ALAT, ASAT, alkaline phosphatases, LDH)
  Blood creatinine, urea
  Blood glucose
  Serum protein, serum albumin, urine glucose
  CA 19-9, ACE
  Pregnancy test for women of childbearing age not using contraception

- **Quality of life questionnaire**
  A QLQ-C30 questionnaire must be completed by the patient on the day consent is signed at the hospital. It can therefore be completed on the same day or in the 15 days prior to randomization.

7.2 Follow-up

Patients will be reviewed weekly or every 2 weeks, depending on the treatment arm.

7.2.1 Arm A: Folfirinox

On D8 of the first cycle
- CBC with platelets, blood creatinine- and potassium levels

Before each cycle: every 14 days
Patients treated with Folfirinox will be reviewed prior to each cycle restart for a clinical evaluation to assess toxicities and determine when treatment should be resumed.
- Assessment of tolerance during intercure
- Check for recovery of any toxicities to initial level or grade ≤1 (except alopecia)
- Complete clinical examination, including weight and WHO
- CBC, platelets
- Quality of life questionnaire
- Serum protein, blood electrolytes, blood creatinine, urea, blood glucose
- Total, free, and conjugated bilirubin (at least monthly)
- Quality of life questionnaire EORTC QLQ-C30

However, depending on tolerance, additional consultation visits may be possible.

All tests revealing treatment-related toxicity must be repeated periodically until toxicity reverses or is presumed irreversible.

7.2.2 Arm B: gemcitabine
Before each administration: every 7 days until D43
Patients treated with gemcitabine will be reviewed before each administration for a clinical work-up to assess toxicities and decide whether to continue treatment.
- Tolerance evaluation
- Check for recovery of any toxicities to initial level or grade ≤1 (except alopecia)
- CBC, platelets

Every 15 days
- Check for recovery of any toxicities to initial level or grade ≤1 (except alopecia)
- Complete clinical examination, including weight and WHO
- CBC, platelets,
- Total, free, and conjugated bilirubin, alkaline phosphatases, AST, ALT
- Urea, blood creatinine
- Blood electrolytes, serum calcium, total protein
- Quality of life questionnaire EORTC QLQ-C30

7.3 Assessments at 8 weeks of treatment (around day 50) for both arms, then every two months
- Complete clinical examination, with assessment of weight, WHO general condition and various toxicities
- **Biological check-up with:**
  CBC, platelets

Complete liver workup (total, free, and conjugated bilirubin, alkaline phosphatase, AST, ALT)
Blood electrolytes, blood glucose
Blood creatinine, urea
Protein levels

- **Tumor markers:**
  ACE, CA 19-9 (only the most significant marker on initial workup: choose the marker with the highest initial value relative to normal)
- **Comparative evaluation of tumor lesions:**
  Thoracoabdomino-pelvic CT scan (depending on initial targets)
- Quality of life questionnaire EORTC QLQ-C30

7.4 Follow-up assessments after resumption of treatment (from D57)

After resumption of treatment, patients will be monitored in the same way as described in Section 7.2, with a quality-of-life questionnaire every 15 days, a CT scan, liver function tests, creatinine levels and an ACE or Ca 19-9 assay every 2 months.

7.5 Follow-up assessments after 6 months of treatment

Progression-free patients who have completed 6 months of treatment will be followed up every 2 months. Quality of life will be assessed by means of the EORTC QLQ-C30 questionnaire, and the duration of response or stabilization by means of imaging.

7.6 Long-term follow-up

Patients who have progressed will be followed every 6 months until death. Long-term toxicity and survival will be assessed. If another treatment is established, it should be reported.

8. EARLY TERMINATION OF TREATMENT

Patients may stop treatment prematurely for the following reasons:

– Toxicity,
– Disease progression,
– Withdrawal of consent,
– Loss of contact for follow-up,
– Major breach of protocol.

As far as possible, patients who have stopped their treatment prematurely will be monitored in the same way as other patients.

9. STUDY ENDPOINTS

9.1 Primary endpoint of Phase II

The best response recorded between the start of treatment and disease progression or the last assessment (best overall response) will be taken into account.
Response is defined according to RECIST criteria (Annex 4).

All objective responses must be confirmed 4 weeks after observation by a new examination.

9.2 Secondary endpoints of Phase II

9.2.1 Toxicity

To be considered evaluable for toxicity, patients must have received at least one infusion of chemotherapy.

- Toxicity is assessed using the NCI toxicity scale version 3.0 (Annex 5).

9.3 Primary endpoint of Phase III

9.3.1 Efficacity

The primary endpoint of this Phase will be overall survival time.

9.4 Secondary endpoints of Phase III

9.4.1 Progression-free survival

Progression-free survival is calculated from the date of randomization to the date of first evidence of documented progression, the date of death, or the date of last news.

9.4.2 Response rate

The best response recorded between the start of treatment and disease progression or the last assessment (best overall response) will be taken into account.

Response is defined according to RECIST criteria (Annex 4).

All objective responses must be confirmed 4 weeks after observation by a new examination.

An independent committee of 2 expert radiologists will review all radiological tumor assessments to confirm the responses recorded.

9.4.3 Toxicity

To be considered evaluable for toxicity, patients must have received at least one treatment course or injection.

- Toxicity is assessed using the NCI toxicity scale version 3.0 (Annex 5).

9.4.4 Quality of life

Quality of life will be measured using the EORTC QLQ-C30 questionnaire (39) (Annex 9), and analyzed in accordance with the specifications of the EORTC Quality of Life Group (43).

The main analysis will focus on those domains of quality of life that are usually the most impaired. The most impaired scales are “overall health/quality of life” (questions 29 and 30), fatigue, pain, physical fitness, psychological state, daily activities (38). Treatment-related changes in “overall health/quality of life” will be considered as the primary objective, and the other criteria as secondary objectives. The other domains of the QLQ-C30 will be analyzed for exploratory purposes only. (43)

The EORTC-PAN 24 questionnaire, specific to pancreatic cancer, will not be used, as it is not yet validated and has not been cross-culturally adapted, making it unsuitable for French-speaking patients.

10. SERIOUS ADVERSE EVENTS

10.0 General definition

Not considered a serious adverse event (SAE):

- Hospitalization <24 hours,
- Hospitalization scheduled prior to the start of the trial and/or provided for in the protocol (biopsy, chemotherapy, etc.).

A Serious Adverse Event (SAE) is any event:

- Resulting in death,
- Life-threatening,
- Resulting in hospitalization or prolongation of hospitalization,
- Causing permanent disability or severe temporary incapacity,
- Causing congenital anomaly, fetal malformation or abortion,
- Medically significant.

The terms *disability* and *incapacity* refer to any temporary or permanent, clinically significant physical or mental handicap affecting the patient’s physical activity and/or quality of life.

Any clinical event or laboratory result considered serious by the investigator and not corresponding to the severity criteria defined above is considered *medically significant*. They may pose a risk to the patient and require medical intervention to prevent an outcome corresponding to one of the aforementioned severity criteria (*examples: overdoses, second cancers, pregnancies, and new events may be considered medically significant*).

10.2 Definition of an expected serious adverse event (SAE-E)

A SAE-E is an event already mentioned in the most recent version of the investigator's brochure, or in the summary of product characteristics (SPC) for drugs with marketing authorization (MA). This definition also applies to the trial drug when it is administered to the same population outside the MA indication.

10.3 Definition of a serious unexpected adverse event (SAE-U)

A SAE-U is an event that is not mentioned or that differs in nature, intensity or evolution from the investigator's brochure or the summary of product characteristics (SPC) for drugs with marketing authorization (MA).

10.4 Intensity criteria

The intensity criteria should not be confused with the severity criteria, which serves as a guide for defining reporting obligations.

The intensity of events will be estimated according to the NCI-CTC version 3.0 classification (Grade 1 to 5 toxicity). The intensity of adverse events not listed in this classification will be assessed according to the following qualifiers:

Mild (Grade 1): does not affect patient's usual daily activity
Moderate (Grade 2): disturbs patient's usual daily activity
Severe (Grade 3): prevents patient's usual daily activity
Very Severe (Grade 4): requires resuscitation/ life-threatening
Death (Grade 5)

10.5 What to do if a serious adverse event occurs

The investigator informs BECT Pharmacovigilance (PV-BECT) of all Serious Expected Adverse Events (SAE-E) and Unexpected Serious Adverse Events (SAE-U), whether or not attributable to the research, which occur during the study or within 30 days of the last treatment administration.

All Delayed Serious Adverse Events (occurring after this 30-day period) considered reasonably related to the protocol treatment(s) or research must be reported without time limit.

Declarations are made by faxing the "Notification of a serious adverse event" form (see Annex 6) to PV-BECT, documenting the event as accurately as possible, dated and signed, within 48 working hours of its discovery:

Bureau d'Etudes Cliniques et Thérapeutiques
Pharmacovigilance
Telephone: 01 44 23 04 16, Fax: 01 44 23 55 70
Email: pv-bect@fnclcc.fr

With regard to each event, the investigator will note:

- Its description as clearly as possible according to medical terminology
- Whether the event is expected or unexpected
- Intensity
- Event start and end dates
- Measures taken and the need for corrective treatment
- Whether trial treatment has been interrupted

- Its progression. In the event of a non-fatal event, the patient's progress should be monitored until they recover or return to their previous state, or until any after-effects have stabilized.
- The causal relationship between this event and the trial treatment or a research-related constraint (period without treatment, additional tests requested for research purposes, etc.)
- The causal relationship with the drug(s) in the trial, the condition being treated, another condition or another treatment

Whenever possible, the investigator should also attach a copy of the report to the serious adverse event report:

- A copy of the hospitalization or extended hospitalization report,
- A copy of the autopsy report,
- A copy of all additional test results, including relevant negative results, together with normal laboratory values,
- Any other document it deems useful and relevant.

All these documents must be anonymized.

Additional information may be requested (by fax, telephone or during a visit) by the instructor.

In the event of an **unexpected SAE reasonably related to one of the study treatments, pharmacovigilance will request additional information from the investigator.** Within **48 hours**, the investigator must send the sponsor a duly completed "**Additional information on an unexpected SAE**" form (see Annex 6-*bis*).

A list of expected SAEs, based on product SPCs, is appended to this protocol (see Annex 12).

In addition, a summary list of expected SAEs, drawn up from the PCR and reclassified according to the NCI-CTC V3 toxicity scale, will be attached to the case report form, to make it easier for the investigator to fill in the SAE form.

Nevertheless, any event that is expected but different in intensity, evolution or frequency will be considered unexpected by pharmacovigilance.

10.6 Monitoring SAEs

The investigator is responsible for the appropriate medical follow-up of patients until resolution or stabilization of the effect, or until the patient's death. **This may sometimes mean that this follow-up extends beyond the patient's discharge from the trial.**

He or she will transmit the additional information to PV-BECT using an SAE declaration form (checking the box "Follow-up no. X" to specify that this is a follow-up and not an initial report) within 48 hours of obtaining it. It also transmits the last follow-up to the resolution or stabilization of the SAE.

He or she will keep the documents concerning the suspected adverse reaction so that, if necessary, he or she can supplement the information previously transmitted.

It responds to requests for further information from PV-BECT in order to document the initial observation.

11. DETERMINATION OF PATIENT NUMBERS AND STATISTICAL ANALYSIS

11.1 Number of subjects required in Phase II

It is decided to conclude that Folfirinox is effective if the objective response rate is greater than or equal to 24%, and to conclude that it is ineffective if this rate is less than or equal to 10%. The number of subjects was calculated using Fleming's multi-stage procedure (27). We decided to include a maximum of 44 subjects in 3 stages per arm, i.e. 88 patients in all (power of 92%, two-sided formulation, 5% threshold).

In the experimental arm (Folfirinox):

♦ At the end of the first stage (20 patients included):
– If 2 or fewer objective responses (ORs) are observed, the trial is stopped, with the conclusion that Folfirinox is not effective.
– If 8 or more objective responses have been observed, will move on to Phase III.
– If between 3 and 7 objective responses are observed, we continue with Phase II: inclusion of 10 additional patients.

♦ At the end of the second stage (30 patients in all):
– If 4 or fewer objective responses are observed, we conclude that Folfirinox is not effective.
– If 11 or more objective responses are observed, we conclude that Folfirinox is effective and proceed to Phase III.
– If between 5 and 10 objective responses are observed, the trial is continued: inclusion of 10 additional patients.

♦ At the end of the third stage (40 patients in all):
– If 6 or fewer objective responses are observed, we conclude that Folfirinox is not sufficiently effective, and we do not proceed to Phase III.
– If there are 12 responses, we will continue the study in Phase III.
– If no conclusion is reached after 40 patients, we will proceed to Phase III, including the number of additional patients.

This design has a power of 0.92 (92 chances out of 100 of concluding efficacy if the objective response rate is equal to 60%). The alpha risk is equal to 0.05 (there are 5 chances out of 100 of concluding that the plan is effective if the non-progression rate is equal to 35%).

11.2 Number of subjects required in Phase III

To demonstrate a difference in median survival of 3 months (from 7 to 10 months median), i.e. a relative risk of 0.70, **360 patients would have to be included** to maintain an overall alpha risk of 5%, accepting a beta risk of 20% (trial power = 80%).This power will be attained when **250 events** have been observed (calculated using East 5 software).

11.3 Statistical analysis

The final statistical analysis should be carried out once **250 events** have been observed.

The data will be presented in the form of:

1. Percentages (qualitative variables),
2. Mean and standard deviation or median and extremes (quantitative variables),

3. Survival curves estimated by the Kaplan-Meier method (survival data) (27). The date of origin will be the date of the draw.

Results for the primary and secondary endpoints will be presented with a 95% confidence interval (Rothman for survival data).

The following will be compared:

1. Categorical variables by a chi-square or by a Fisher test,
2. Quantitative variables with a Student's t-test or a non-parametric test (Wilcoxon),
3. Survival data by a log-rank test.

These comparisons will be adjusted for stratification factors.

All tests will be two-tailed at the 5% threshold.

Statistical analyses will be carried out using Stata v10 software.

11.4 Non-compliance with protocol

No exclusion will be accepted. Incorrectly included subjects and subjects who fail to comply with the protocol will be included in the analysis according to their randomization group (intention-to-treat analysis). In order to limit the number of patients lost to follow-up, the investigator at each center will be responsible for reconvening patients who fail to attend surveillance consultations.

11.5 Intermediate analyses and monitoring of the trial

An interim efficacy analysis will be carried out when 2/3 of events (deaths) have been observed, i.e. **167 events.** In order to maintain an overall risk of 5%, this intermediate analysis will only be considered significant if the p-value is less than or equal to 0.001 and **p ≤0.049** at the final analysis.

The Monitoring Committee (IDMC) may propose premature termination of the trial if it deems this necessary, and if the totality of available data from the trial or other sources is sufficiently convincing to influence the therapeutic practices of the majority of physicians.

12. RESEARCH COSTS AND EXTRA COSTS

Any additional costs referred to in article R.1121-1 of the French Public Health Code are covered by an agreement negotiated between the FNCLCC and the establishment's representative, taking into account the financial resources available to the FNCLCC for its public sponsorship activities.

However, the FNCLCC is responsible for organizing the trial and supplying the following materials: protocol, observation booklet, investigator file, as well as the study products irinotecan and oxaliplatin.

Equipment, treatments or services provided by other partners must be specified in the trial agreement.

13. QUALITY ASSURANCE AND INDEPENDENT COMMITTEE

The sponsor is responsible for implementing a quality assurance system, as described in federal procedures, to ensure that the trial is carried out in accordance with the protocol and GCP. A centralized review of the efficacy endpoint will be carried out by a committee of independent experts.

14. "PRODIGE" PUBLICATION RULES

Prompt publication of PRODIGE trials by a quality journal is an essential objective for the progress of therapeutics. Publication is the responsibility of the PRODIGE Coordination Committee (PCC), which takes the final decision:

– the timing of publication of a study's preliminary and final results
– the composition of an Editorial Committee (maximum 5 members)

All information resulting from trials is considered confidential, at least until appropriate analysis and inspection by the sponsor, coordinating investigator, and trial statistician have been completed.

The PRODIGE Coordinating Committee (PCC) may delegate these functions to the trial coordinator.

In all cases, the PCC validates the choices made and ensures that deadlines are met. In the absence of a response from the PCC within one month of submission to the Editorial Committee, the project is deemed to have been accepted.

1) The Editorial Committee comprises:

- The coordinator (or coordinators if there are two) who wrote the first project. They will be the main writer, except in exceptional cases.
- The statistician(s) who carried out the data analysis
- The most important contributors
- Possibly a specialist who has made an essential contribution to data analysis (biologist, pathologist, etc.)

2) The Principal Editor undertakes to submit for publication within a period determined by the PCC. This period should not exceed one year after the close of a trial. If they are unable to do so, the PCC will appoint a new editor who will become the first author. To assist with the writing of trial articles, a medical editor may be called in and writing workshops organized for the senior editor, in collaboration with the statistician. Before any publication, the list of inclusions by center and the list of investigators for each center for the trial in question will be made available to the trial investigators.

3) The authors of the publication are, in order according to the work performed and the number of included patients:

- Principal Editor
- Members of the Editorial Committee (see above)
- A limited number of investigators (one per center) in the order of their participation, and as a rule only one per center; but for certain centers, the Management Committee may decide on two investigators. This rule may be weighted to allow certain small and medium-sized centers that have made a major effort to be included among the authors. The PCC will validate this weighting to ensure that no one is disadvantaged.
- The maximum number of authors authorized by the journals will be used.
- Whatever the number of patients included, there will be at least one author representing one of the two partners (FFCD or FNCLCC).
- In the case of a derivative publication or ancillary work, the authors may be different from those of the original article and reflect the specialty concerned by the article, for example:

in RCT trials, an article dedicated to radiotherapy may be signed by radiotherapists who are co-investigators in the centers that included the subjects. The last author of this derivative publication (possibly “equally contributed”) is the first signatory of the original article.

- The Prodige partnership is mentioned in the title or after the authors. In the case of cooperative trials, the first association cited is the one that initiated the trial, and the others are mentioned provided they have included at least 5% of patients, in the order of their participation.
- With a few exceptions, for trials sponsored or managed by the FFCD, a member of the Inserm U 866 unit will be the last author, if he or she is not the main editor, to ensure that the work is taken into account by Inserm. In this case, the penultimate author may be indicated as having "equally contributed," if this is applicable to the journal concerned.
- The statistician will be among the authors, as a rule above the third place. He may be the first or second author of a specific publication.

All participants not listed among the authors are cited at the end of the article. The data manager is also cited. He may be included in the authors’ list if the PCC deems it justified.
The partners are thanked.
Authors and the sponsor receive a manuscript for review before it is sent to a journal. They undertake to reply within 15 working days for their opinion to be taken into account (30 days during the summer).

4) <u>Oral presentation of trial results</u>:

An investigator may, with the agreement of the PCC and the Management Committee, present all or part of his or her results as an oral communication. As a general rule, the authors are the same as for the written article, but the order of authors for articles and communications may vary, and may also vary according to the congress where the communication is made. In certain cases (multidisciplinary studies, or pathological, biological or echo-endoscopic studies parallel to a therapeutic trial, for example), other authors may be chosen on the basis of their work. The PRODIGE partnership and other associations should be cited where appropriate.

15. ETHICAL AND REGULATORY ASPECTS

The clinical trial must be conducted in accordance with the ethical principles of the Helsinki Declaration of 1964, revised in Edinburgh in 2000, the Good Clinical Practices of the International Conference on Harmonization (ICH-E6, 7/17/96), the European Directive (2001/20/EC) on the conduct of clinical trials, the amended Huriet Act (12/20/98) on the Protection of Persons undergoing Biomedical Research, and the provisions of the Commission Nationale Informatique et Libertés [French Data Protection Authority] (law no. 94-548 of 7/1/94 supplementing law no. 78-17 of 1/6/78).

15.1 Consultative Committee for the Protection of Individuals in Biomedical Research (CCPPRB)

The clinical trial protocol and any amendments, information or documents deemed necessary by the sponsor are submitted by the investigator coordinating the trial to a CCPPRB in the region where they operate (Article L. 1123-6). The various originals of the written responses from the CCPPRB must be forwarded by the coordinator to the sponsor.

15.2 Information and consent of participants

Before any biomedical research is carried out on a person, that person's free, informed, and express consent must be obtained after the investigator or the investigator's representative has informed them of the purpose of the research, the progress and duration of the study, the benefits, potential risks and constraints of the trial, the nature of the product studied, and the opinion given by the CCPPRB (Article L. 1122-1).

The consent form must be dated and signed personally by the patient and the investigator or the physician who represents the latter (the original will be archived by the investigator, and a copy given to the patient or the latter's legal representative).

The patient information and informed consent form (Annex 7) must be combined on the same document, to avoid any risk of dispute over the content of the information given.

15.3 Investigator responsibilities

The principal investigator of each institution involved undertakes to conduct the clinical trial in accordance with the protocol approved by the CCPPRB. The investigator must not make any changes to the protocol without the sponsor's authorization, and without the CCPPRB having given a favorable opinion on the proposed modifications.

It is the responsibility of the principal investigator to:

– provide the sponsor with their curriculum vitae and those of the co-investigators,
– identify the team members involved in the trial, and define their responsibilities,
– start recruiting patients after authorization from the sponsor,
– make every effort to include the required number of patients within the established recruitment period.

It is the responsibility of each investigator:

– obtain the patient's dated and personally signed informed consent prior to any trial-specific selection procedure,
– regularly complete the case reports for each patient included in the trial, and give the Clinical Research Assistant (CRA) direct access to the source documents so that they can validate the case report data,
– date, correct, and sign the corrections to the case reports for each patient included in the study,
– accept regular visits from CRAs and, if necessary, from auditors appointed by the sponsor or inspectors from the supervisory authorities.

All documentation relating to the study (protocol, consents, observation notebooks, investigator file, etc.), as well as original documents (laboratory results, X-rays, consultation reports, reports of clinical examinations carried out, etc.) must be kept in a safe place and treated as confidential material. Data archiving is the responsibility of the investigator, in accordance with current legislation.

The latter must keep the data a list identifying the patients for a minimum of 15 years after the end of the study.

15.4 Responsibilities of the sponsor

In accordance with the Huriet Act, it is the sponsor's responsibility to:

– take out insurance to cover civil liability in the event of any harmful consequences of the research for the person carrying it out (Article L.1121-7),

– pay a fixed fee to the relevant DRASS [Regional Health and Social Affairs Department] for consultation of a personal protection committee (CCPPRB) (Decrees of 5/7/91 and 12/13/01),

– send the initial declaration of intent describing the essential data of the research to the Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS) [French Health Products Safety Agency], together with the opinion of the CCPPRB (Article L.1123-8),

– inform the Directors (Article L.1123-10, R.5124) and Pharmacists (Article L.5125-19, R.5124-1) of healthcare establishments,

– provide investigators with all the information they need to conduct the research (Article R.5122),

– inform the AFSSAPS of any Serious Adverse Event likely to be due to the research, as soon as it is known, and of any premature termination of the study (Article L.1123-8).

The sponsor must also file a declaration of nominative and computerized medical data with the Advisory Committee and the Commission Nationale Informatique et Libertés (CNIL) [French Data Protection Authority], in accordance with the conditions for application of the simplified procedure (Law no. 94-548 of 7/1/94 supplementing Law no. 78-17 of 1/6/78).

The sponsor must ensure that essential documents relating to the conduct of the study are archived in conditions that guarantee their security, for the minimum period stipulated by GCP, i.e. 15 years after the end of the research.

15.5 Patients' Committee

In the context of clinical trials in oncology sponsored by the FNCLCC, the Patients' Committee undertakes to review the protocol and suggest improvements, particularly in terms of the quality of the information letter, the provision of a treatment and monitoring plan, and suggestions for measures to improve patient comfort, in accordance with the charter drawn up between the Patients' Committee of the Ligue Nationale Contre le Cancer (LNCC) and the BECT of the FNCLCC.

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ANNEXES

ANNEX 1:
Product preparation and administration methods

1 – IRINOTECAN (CAMPTO)

Irinotecan is a semi-synthetic derivative of camptothecin. It acts as an antineoplastic agent that acts as a specific inhibitor of DNA topoisomerase I. Irinotecan is metabolized by carboxylesterase in most tissues into an active metabolite, SN-38, which has been shown to be more active than irinotecan on purified topoisomerase I and more cytotoxic on several murine and human tumor cell lines. The inhibition of DNA topoisomerase I by irinotecan or SN-38 induces single-strand DNA lesions that block the DNA replication fork and are responsible for the cytotoxic activity. This is a function of the contact time with the cells and is specific to the S phase.

Presentation
Solution to be diluted for infusion, concentrated in vials containing 40 mg and 100 mg in 2 ml and 5 ml, respectively, providing a 20 mg/ml solution.

Preparation
To prepare the Campto solution , withdraw, with the aid of a graduated syringe, the desired amount of Campto solution from the bottle, making sure to respect aseptic conditions, and inject it into a 250 ml infusion flask containing either a 0.9% sodium chloride solution or a 5% glucose solution. Thoroughly mix the solution to be infused by manual rotation.

Storage
The product must be stored away from light.
After reconstitution, the Campto solution contains no preservatives, so it must be used immediately after dilution. However, if the dilution is performed under strict aseptic conditions, the Campto solution for infusion can be used (including infusion time) within 12 hours, stored at ambient temperature, or for 24 hours, stored in the refrigerator (+ 2º to + 8ºC) after preparation.

2 – OXALIPLATIN (ELOXATIN)

Oxaliplatin is an antineoplastic agent, belonging to a new class of platinum in which the platinum atom is complexed with 1,2 diaminocyclohexane (DACH) and an oxalate group. Oxaliplatin is a single enantiomer, cis-[oxalate (trans 1-1-1,2-DACH) platinum]. Oxaliplatin presents with a broad spectrum of cytotoxic activity in vitro and anti-tumor activity in vivo in various tumor model systems, including human colorectal cancer models. Oxaliplatin has also been shown to be effective, both in vitro and in vivo, in various cisplatin-resistant cell lines. A synergistic cytotoxic action with 5-fluorouracil has been demonstrated in vitro and in vivo. Although not fully elucidated, studies on the mechanism of action show that the hydrated derivatives resulting from the biotransformation of oxaliplatin interact with DNA to form intra- and inter-strand bridges leading to an interruption of DNA synthesis, causing the cytotoxic and anti-tumor activity.

Presentation
concentrated solution for infusion dosed at 50 mg and 100 mg.

Preparation
Reconstitution in water or 5% glucose solution for injection, obtaining a solution containing 5 mg of oxaliplatin per ml
To obtain an oxaliplatin concentration of 5 mg/ml, add 10 ml of solvent to the 50 mg concentrated solution and 20 ml of solvent to the 100 mg concentrated solution.

Storage
Under conditions of use, physicochemical stability has been demonstrated for 48 hours at +2°C to +8°C and at +30°C. From a microbiological point of view, the reconstituted solution must be diluted immediately into a 5% glucose solution. If dilution is not carried out immediately, the user is responsible for storage times and conditions prior to use; in-use storage times normally should not exceed 24 hours at +2°C to +8°C, except if reconstitution has taken place in controlled and validated aseptic conditions.

3 – 5-FLUOROURACIL

Fluorouracil is a cytostatic antineoplastic agent in the antimetabolite (antipyrimidine) class. To better understand the activity of fluorouracil, it should be remembered that uracil plays a fundamental dual role in rapidly growing tissues: on the one hand, by being the precursor (via thymidylate synthase) of thymine, a base necessary for the synthesis of DNA that presides over cell division; on the other hand, by entering into the composition of RNA structures that preside over the synthesis of proteins and cellular enzymes.

Presentation
Solution to be diluted for infusion, concentrated in vials containing 250, 500 mg, 1g and 5 g in 5 ml, 10 ml, 20 ml and 100 ml respectively, providing a 50 mg/ml solution.

Method of administration
Intravenous route. Do not administer intramuscularly. In the event of extravasation, administration will be stopped immediately.
Dilutions: 15 ml of solution for injection can be mixed with 250 ml of the following solutions:
- 0.9% sodium chloride
- 5% glucose
- 10% glucose
- 2.5% glucose + 0.45% sodium chloride
- Ringer's solution
- Hartmann's solution

Storage
Store at a temperature between +15ºC and +25ºC. This medicine is sensitive to light. Keep the primary packaging in the outer carton.
After dilution, immediate use is recommended. However, stability has been demonstrated for 8 hours at a temperature between +15ºC and +25ºC.

4 - L-FOLINIC ACID

Anti-anemic (B: blood and hematopoietic organs). In its levorotatory form, folinic acid represents the active form of DL-folinic acid. A dose of the L-isomer corresponds to one-half the dose of the DL racemic compound. The efficacy and adverse effects of the L-isomer are identical to those of the racemic compound.
Folinic acid is an anti-anemic factor derived from folic acid, of which it represents the active metabolite. It is a biochemical antagonist of antifolate agents such as methotrexate (of which it is the specific inhibitor), but also of pyrimethamine and, to a lesser extent, salazopyrine.

Presentation
The product is supplied in the form of lyophilisate for parenteral use at a dosage of 25 mg and as a solution for IM or IV injection at a dosage of 25 mg/2.5 ml.

Storage
The lyophilisate should be stored below 30ºC and protected from light and moisture. After reconstitution, the solution can be stored for 24 hours at a temperature below 30ºC. The solution should be stored in a refrigerator from 2ºC to 8ºC and protected from light.

5 – GEMCITABINE (GEMZAR)

Presentation
Gemcitabine is supplied in the form of a lyophilized powder packaged in sterile vials containing 200 mg or 1 g of gemcitabine hydrochloride (expressed in the form of a free base), mannitol and sodium acetate.

Preparation
The recommended diluent for reconstitution of Gemzar® is a 0.9% sodium chloride solution.
Vials will be reconstituted by adding isotonic saline to obtain a solution ideally containing 10 mg/ml maximum. The concentration for 200 mg and 1 g vials should not exceed 40 mg/ml.

Administration
An appropriate amount of the product will be prepared with isotonic saline and administered by continuous infusion for 30 minutes.

Storage
The lyophilized product should be stored below 3ºC. Once the product has been reconstituted, it should be stored at room temperature and used within 24 hours. Do not store the reconstituted product in the refrigerator.

ANNEX 2:
Summary table of investigations

Treatment plan														
Date	**D1**	**D8**	**D15**	**D22**	**D29**	**D36**	**D43**	**D50**	**D57**	**D64**	**D71**	**D78**	**Dn**
Arm A: Folfirinox	**C1**		**C2**		**C3**		**C4**		**C5**		**C6**		**Cn**
	oxaliplatin 85 mg/m2 D1+ irinotecan 180 mg/m2 D1+ folinic acid 400 mg/m2 D1, 5-FU bolus 400 mg/m²D1, 5-FU continuous 2.4 g/m2 over 46 hours D1/ D2 of each cycle								*Resumption of treatment according to the previous schedule, every 2 weeks*				
Arm B: gemcitabine													
	gemcitabine 1000 mg/m² every week for 7 weeks								*Resumption of gemcitabine 3 weeks out of 4*				

12 cycles planned for Arm A = 6 months of treatment

ARM A Folfirinox monitoring plan									
Visit	**Inclusion analysis**	**Follow-up analysis**				**8-week analysis**	**Follow-up analysis after resumption**		
Visit No.	**V0**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**Vn**
Date	**D0**	**D1**	**D15**	**D29**	**D43**	**Around D50**	**D57**	**D71**	**Dn**
Signed informed consent	**X**								
Criteria for inclusion / non-inclusion	**X**								
Randomization	**X**								
Clinical examination									
Weight	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**
Body surface area	**X**								
Overall Status / WHO	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**
Concomitant treatments	**X**								
Toxicities (2)									
Tolerance evaluation			**X**	**X**	**X**	**X**	**X**	**X**	**X**
Biological examination (4)									
FBC, platelets	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
PT, KCT	**X**								
Electrolyte panel, Ca	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**
Serum total protein	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**
Total albumin, LDH	**X**								
Hepatic assessment	**X**		**X****	**X****	**X****	**X**	**Examination every two months**		
Serum creatine level	**X**	**X**	**X**	**X**	**X**	**X**	**Examination every two months**		
Blood sugar level	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**
CEA, Ca 19-9 *	**X**					**X**	**Examination every two months**		
Pregnancy test	**X**(1)								
Paraclinical assessment(3)									
Thoracic, abdominal, pelvis CT scan	**X**					**X**	**Scan examination every 2 months**		
ECG	**X**								
Quality of Life Questionnaire	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**

6 months of treatment expected for Arm B

ARM B gemcitabine monitoring plan													
Visit	**Inclusion analysis**	**Follow-up analysis**							**8-week analysis**	**Follow-up analysis after resumption**			
Visit No.	**V0**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**Vn**
Date	**D0**	**D1**	**D8**	**D15**	**D22**	**D29**	**D36**	**D43**	**Around D50**	**D57**	**D64**	**D71**	**Dn**
Signed informed consent	**X**												
Criteria for inclusion / non-inclusion	**X**												
Randomization	**X**												
Clinical examination	**X**												
Weight	**X**	**X**		**X**		**X**		**X**	**X**	**X**		**X**	
Body surface area	**X**												
Overall Status / WHO	**X**	**X**		**X**		**X**		**X**	**X**	**X**		**X**	
Concomitant treatments	**X**												
Toxicities (2)													
Tolerance evaluation			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Biological examination (4)													
FBC, platelets	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
PT, KCT	**X**												
Electrolyte panel, Ca	**X**			**X**		**X**		**X**	**X**	**X**		**X**	
Serum total protein	**X**								**X**				
Total albumin, LDH	**X**												
Hepatic assessment	**X**			**X**		**X**		**X**	**X**	**Examination every two months**			
Serum creatine level	**X**			**X**		**X**		**X**	**X**	**Examination every two months**			
Blood sugar level	**X**			**X**		**X**		**X**	**X**	**X**		**X**	
CEA, Ca 19-9*	**X**								**X**	**Examination every two months**			
Pregnancy test	**X**(1)												
Paraclinical													
Thoracic, abdominal, pelvis CT scan	**X**								**X**	**Scan examination every 2 months**			
ECG	**X**												
Quality of Life Questionnaire	**X**			**X**		**X**		**X**	**X**	**X**		**X**	

**Only the highest-performing marker will be measured later on; choose the marker that has the highest initial value compared to the normal value.*

*** Hepatic assessment with total, free and conjugate bilirubin must be done at least once (1) a month.*

(1) for persons of childbearing age without effective contraceptive means.

(2) Serious Adverse Events (SAE) are to be declared to the sponsor within 48 hours up to 30 days after the end of the last course of chemotherapy. Beyond that period, only those SAEs likely to be due to the research will be declared to the sponsor when no cause other than the research could be reasonably attributed thereto.

(3) The radiological assessment can be done during the 3 weeks prior to inclusion. (4) The biological assessment must be done no later than one week prior to inclusion.

Patients without progression who have had 6 months of treatments will be followed up on every 2 months. The quality of life will be evaluated by sending the EORTC QLQ-C30 questionnaire, as will the progression of the disease, thanks to imaging.

Patients who have had progress will be followed up on every 6 months until death. The following will be evaluated: long-term toxic effects and survival. If another treatment is established, it must be reported.

ANNEX 3:
Evaluation of the overall status based on the ECOG or WHO scale

OVERALL STATUS ECOG-ZUBROD/WHO	SCALE
Normal activity, without restrictions.	**0**
Restricted in physically strenuous activity but ambulatory and able to carry out light work.	**1**
Ambulatory and capable of all selfcare but unable to carry out any work activities for more than 50% of waking hours.	**2**
Capable of only limited selfcare. Confined to bed or chair more than 50% of waking hours.	**3**
Completely disabled. Cannot carry on any selfcare. Patient is totally confined to bed or chair.	**4**

ANNEX 4:
Classification of tumor evaluations
RECIST Classification (JNCI, 2/2/2000)

1. Measurement of tumor lesions

1.1 Definitions

Tumor lesions will be divided into two broad categories:

Measurable lesions: lesions that can be measured precisely in at least one dimension (the largest diameter being reported), whether ≥ 20 mm with a conventional scanner or≥ 10 mm with a spiral scanner.

Non-measurable lesions: all other lesions comprising small lesions with larger diameters < 20 mm with a conventional scanner or < 10 mm with a spiral scanner and truly non-measurable lesions.

All measurements must be reported using the metric system by using a ruler or calipers. Baseline assessments should be carried out as soon as possible (not exceeding 4 weeks) after the start of treatment.

Lesions that are considered truly non-measurable are as follows:

- Bone lesions
- Meningeal involvement
- Ascites
- Pleural and/or pericardial effusion
- Inflammatory breast
- Cutaneous and/or pulmonary lymphangitis
- Abdominal masses that are not confirmed or followed up on by an imaging technique
- Cystic lesion

Tumor lesions located in irradiated territory may be considered measurable or non-measurable depending on the conditions defined in the protocol.

1.2 Measurement methods

The measurement method and technique used for lesion measurements must be identical at the start of the study and during follow-up. Imaging evaluations are preferred to clinical evaluations when both methods have been used to determine the anti-tumor activity of the treatment.

Clinical lesions
Clinical lesions will be considered measurable when they are superficial (skin nodule, palpable lymph node). For cutaneous lesions, documentation via color photograph with a ruler to assess the size of the lesion is recommended.

Pulmonary X-ray
Lesions visible on pulmonary X-rays are considered measurable when they are clearly identified and surrounded by pulmonary air. However, a CT scan is preferred.

CT scan and MRI
CT scans and MRIs are currently the most reproducible techniques for measuring target lesions and evaluating response. Conventional CT scans and MRIs are performed with contiguous slices at least 10 mm thick. Spiral CT scans should be performed using contiguous 5 mm slices.
This applies to the thorax, abdomen and pelvis. The head, neck and extremities require specific protocols.

Ultrasound
When the goal of the study is the evaluation of an objective response, ultrasound should not be used to measure tumor lesions that are not clinically easily accessible.
Ultrasound can be an alternative to clinical examination to measure palpable superficial lymph nodes, subcutaneous lesions and thyroid nodules. Ultrasound can be used to confirm complete disappearance of superficial lesions evaluated by clinical examination.

Endoscopy, laparoscopy
The use of these techniques to evaluate an objective response is not fully validated. Their use in this specific context requires sophisticated equipment and a level of expertise that is available in only a few centers.
Their use to evaluate objective responses should be restricted to the validation of studies in reference centers. However, such techniques can be used to confirm a complete response on the pathological level when biopsies are performed.

Tumor markers
Tumor markers cannot be used by themselves to evaluate a response.
If markers are initially above their normal value, they should be normalized when the patient is considered in complete response and when all tumor lesions have disappeared.
Additional criteria for standardizing the use of PSA and CA-125 are currently being validated and can be used in clinical trials.

Cytology and histology
In rare cases, these techniques can be used to differentiate a partial response and a complete response. For example, they can be used in germ cell tumors where a benign residue may persist.
Cytological confirmation of the neoplastic origin of an effusion that appears or is aggravated during treatment is necessary to differentiate tumor response, stability and progression when a measurable tumor is a necessary criterion to assess tumor response (an effusion may be a side effect of treatment).

2. Evaluation of tumor response

2.1 Evaluation upon inclusion

Determination of overall tumor response and of measurable lesions
To evaluate an objective response**,** the tumor mass must be assessed at the start, and comparative measures must be made during the follow-up.
Only patients presenting with measurable disease upon inclusion can be included in protocols where tumor response is the primary evaluation criterion. A measurable disease is defined as the presence of at least one measurable lesion. If the measurable disease is limited to a single lesion, its neoplastic nature should be confirmed by cytology/histology.

Documentation of target/non-target lesions upon inclusion
All measurable lesions and up to a maximum of 5 lesions per organ and 10 in total, representative of all affected organs, should be considered target lesions, noted and measured upon inclusion. Target lesions should be selected based on their size (largest diameter) and the possibility of being accurately measured in a reproducible manner (whether by imaging or clinically). The sum of the largest diameters of all target lesions calculated upon inclusion will be used as a reference to assess a tumor response. All other lesions or sites of disease should be noted and identified as non-target lesions upon inclusion. They do not need to be measured. During follow-up, they will be noted as present or absent.

2.2 Response criteria

Evaluation of target lesions

Complete response (CR): disappearance of all target lesions.
Partial response (RP): decrease of at least 30% of the sum of the largest diameters of the target lesions compared to the sum of the largest diameters of the target lesions upon inclusion.
Progression (PD): increase of at least 20% of the sum of the largest diameters of the target lesions, taking as a reference point the smallest value of the sum of the largest diameters reported since the start of treatment or appearance of one or more new lesions.
Stable disease (SD): no decrease or increase sufficient to be considered a partial response or progression in reference to the smallest sum of the largest diameters since the start of treatment.

Evaluation of non-target lesions
Complete response : disappearance of all non-target lesions and normalization of tumor markers.
Incomplete response and stable disease: Persistence of one or more non-target lesions and/or persistence of tumor markers above normal values.
Progression: appearance of one or more new lesions. Unequivocal progression of existing non-target lesions.

Evaluation of the best overall response
The best overall response is the best response recorded from the start of treatment until recurrence or progression takes place (taking the smallest measurement reported since the start of treatment as the reference for progression).

In general, the best patient response will depend on all measurements and the reconciliation of criteria defined in Paragraph 2.2.

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	no	CR
CR	Incomplete response and stable disease	no	PR
PR	no - PD	no	PR
SD	no - PD	no	SD
If a target or non-target lesion progresses or if a new lesion appears, the evaluation of the overall response is the progression of the disease.			

Patients presenting with changes in their condition requiring interruption of treatment without obvious objective disease progression should be noted at this time as symptomatic deterioration. Maximum effort should be made to assess progression even after discontinuation of treatment.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When this distinction is involved in the evaluation of a complete response, it is recommended to explore the residual lesion by needle biopsy and/or cytology before confirming a complete response.

2.3 Confirmation of the measurement/ duration of the response

Confirmation

To give partial response or complete response status, changes in tumor measurements must be confirmed by new measurements at least 4 weeks after the first response was observed.

In the case of stable disease, measurements can meet this criterion only once after study entry for at least a minimum time interval (usually no fewer than six to eight weeks).

Duration of the overall response

The duration of the overall response is determined from the time at which a complete response/partial response is achieved (the first reported) until the time at which recurrence/progression is objectively documented.

The duration of the complete response is determined from the time at which a complete response is achieved until the time at which objective recurrence is documented.

Duration of stable disease

Stable disease is defined from the start of treatment until a progression criterion is met, taking the smallest total of measurements reported since the start of treatment as a reference point.

The clinical relevance of the duration of stable disease varies based on the types of tumor types and their grades. However, it is recommended to specify in the protocol the minimum time interval required between two measurements to determine the stability of the disease. This time interval should take into account the expected clinical benefit that such a status can bring to the population being studied.

2.4 Progression-free survival

This document primarily concerns the use of objective responses. In certain cases (brain tumors, anticancer drug trials), evaluation of tumor response may not be the optimal method to estimate the potential anti-tumor activity of new agents/regimens. In such cases, progression-free survival may be considered as a valid alternative to provide an initial estimate of the biological effect of new agents that may act by non-cytotoxic mechanisms. It is clear that in an uncontrolled trial proposing to use progression-free survival, it will be necessary to carefully document the data to estimate the expected progression-free survival in the absence of effective treatment. It is also recommended that the analysis be very conservative in light of the likelihood of creating confusion from biases concerning, for example, selection or estimation. Uncontrolled trials using progression-free survival as a primary objective should be considered on a case-by-case basis, and the methodology to be applied should be fully described in the protocol.

2.5 Review committee

For studies where the response rate is the primary objective, it is strongly recommended that all responses be reviewed by an expert independent from the study. A simultaneous review of patients' records and radiological images is the best approach.

ANNEX 5:
Extract of toxicity criteria (CTC–NCI)
Version of 5/31/2003

ANNEX 6:
Form for notification of a severe adverse event

NOTIFICATION OF A SEVERE ADVERSE EVENT

To be faxed to the BECT pharmacovigilance No. + 33 (0)1 44 23 55 70

[Clinical Oncology Investigation Center]
Centre d'Investigation Clinique en Cancérologie
F.N.C.L.C.C.

EudraCT No.: …… **Protocol No. :** …… **Country :**……

□ **EXPECTED Severe Adverse Event** □ **UNEXPECTED Severe Adverse Event**

□ **Initial Report** □ **Follow-up report** **No.**: |__| **Investigative center :** ..... ……

(1) According to the RCP (Vidal) or BI (most recent version)

1. PATIENT DETAILS

Inclusion No.: |_____|	Surname (3 letters): |__|__|__|	First name (2 letters): |__|__|	Date of birth: |__|__| / |__|__| / |__|__|__|__|
Sex: □ F M □	Weight (kg): |_____|	Height (cm): |_____|	Treatment arm: |____|

2. EVENT DETAILS

Date event : |__|__| / |__|__| / |__|__| **Toxicity (grade NCI – CTC V3):** □ **1** □ **2** □ **3** □ **4** □ **5**

Diagnosis or primary symptoms… ……

……

3. TYPE OF EVENT

□ Death …… date |__|__| / |__|__| / |__|__| Temporary or permanent disability / incapacity

□ Life-threatening prognosis □ Other cancer: ……

□ Hospitalization (> 24h) or hospitalization extension) date |__|__| / |__|__| / |__|__| Congenital anomaly or fetal defect

□ Medically significant, please specify: ……

4. DEVELOPMENT

□ Current event Death related to the event □

□ Resolution without side effect, date |__|__| / |__|__| / |__|__| Death unrelated to the event □

□ Resolution with side effects, date |__|__| / |__|__| / |__|__| Unknown □

Type of side effects: … …… End of hospitalization date: |__|__| / |__|__| / |__|__|

5. TREATMENTS

DATES OSES AND UNITS MPUTABILITY D I

CHEMOTHERAPY, RADIOTHERAPY, ETC. OUTER		Treatment dates prior to appearance of the event		Last dose administered	Cumulative doses since the 1st administration	1: Excluded 2: Doubtful 3: Plausible 4: Likely 4: Very likely 6: Cannot be concluded
1.		From|__|__|__|__|__|	to|__|__|__|__|__|			|__|
2.		From|__|__|__|__|__|	to|__|__|__|__|__|			|__|
3.		From|__|__|__|__|__|	to|__|__|__|__|__|			|__|
4.		From|__|__|__|__|__|	to|__|__|__|__|__|			|__|
5.		From|__|__|__|__|__|	to|__|__|__|__|__|			|__|

Have any of the treatments been stopped?

□ Yes No. |__| No. |__| No. |__| No. |__| No.|__| □ No NA □

Has the event disappeared after stopping any of the products?

□ Yes No NA □

Have any of the treatments been reintroduced?

□ Yes No. |__| No. |__| No. |__| No. |__| No.|__| □ No NA □

Has the event reappeared after reintroduction?

□ Yes No □ □NA

6. OVERALL IMPUTABILITY *(According to you, this event is highly linked)*

□ to the treatment(s) under trial (*specify the name(s) of the treatments*)…… to the progression of the disease

□ to the trial protocol □ other concomitant disease(s)

□ other concomitant treatment(s) □ other(s):……

7. NOTIFIER

Name and position of the notifier:

Establishment:
Address:
Telephone:
Fax:
E-mail:

Date |__|__| / |__|__| / |__|__|

Signature of the investigator/co-investigator

ANNEX 6 bis:
Additional information form for an unexpected SAE

ADDITIONAL INFORMATION
ON AN UNEXPECTED SEVERE ADVERSE EVENT To be faxed to the BECT pharmacovigilance No. + 33 (0)1 44 23 55 70

[Clinical Oncology Investigation Center]
Centre d'Investigati Clinique e Cancérolo

EudraCT No.: .... **Protocol No.:** .... **Country :**............ ....

□ **Follow-up report No.**: |__| **Investigative center:** ……………………………….............

(1) According to the RCP (Vidal) or BI (most recent version)

1. PATIENT DETAILS

Inclusion No.: |__________|	Surname (3 letters): |__|__|__|	First name (2 letters): |__|__|	Date of birth: |__|__| / |__|__| / |__|__|__|__|
Sex: □ F M□	Weight (kg): |______|	Height (cm): |______|	Treatment arm: |____|

2. EVENT DETAILS
Date event : |__|__| / |__|__| / |__|__| **Toxicity (grade NCI – CTC V3): 1 2 3 4 5**

Diagnosis or primary symptoms……………………………………………………………………………………………..

....

3. NARRATIVE
....

....

....

4. DEVELOPMENT
□ Current event
□ Resolution without side effect, date |__|__| / |__|__| / |__|__|
□ Resolution with side effects, date |__|__| / |__|__| / |__|__|
Type of side effects: ... .

□ Death related to the event
□ Death not related to the event
□ Unknown
End of hospitalization date: |__|__| / |__|__| / |__|__|

5. TREATMENTS *(complete the table below on page 2/2)*

6. TREATMENT OF ADVERSE EVENT

Treatment	Dose/Unit	Route	Indication	Start Date	End date	Ongoing
....			....	|__|__| / |__|__| / |__|__|	|__|__| / |__|__| / |__|__|	
....			....	|__|__| / |__|__| / |__|__|	|__|__| / |__|__| / |__|__|	
....			....	|__|__| / |__|__| / |__|__|	|__|__| / |__|__| / |__|__|	

7. PERTINENT CONCOMITANT MEDICATION *(excluding that used for treating the event)*

Treatment	Dose/Unit	Route	Indication	Start date	End date	UNDER WAY	Causal relationship	
							yes	no
....			....	|__|__| / |__|__| / |__|__|	|__|__| / |__|__| / |__|__|			
....			....	|__|__| / |__|__| / |__|__|	|__|__| / |__|__| / |__|__|			
....			....	|__|__| / |__|__| / |__|__|	|__|__| / |__|__| / |__|__|			

8. PERTINENT MEDICAL HISTORY AND/OR CONCOMITANT DISEASE(S)
....…............ ....

....………..……...

9. OVERALL IMPUTABILITY *(According to you, this event is highly linked)*
□ to the treatment(s) under trial (*specify the name(s) of the treatments*)... .... to the progression of the disease
□ to the test protocol   □ to other concomitant treatment(s)
□ other concomitant treatment(s)   □ other(s)...

10. NOTIFIER
Name and position of the notifier:

Establishment:
Address:
Telephone:
Fax:
E-mail:

Date |__|__| / |__|__| / |__|__|

Signature of the investigator/co-investigator

<u>ADDITIONAL INFORMATION</u> FOR AN UNEXPECTED SEVERE ADVERSE <u>EVENT</u> (page 2/2)

To be faxed to the BECT pharmacovigilance No. + 33 (0)1 44 23 55 70

Protocol No.: ***EudraCT No.:*** ***Patient No.:***

5. TREATMENTS

<table>
<tr><th></th><th>ROUTE</th><th colspan="2">DATES</th><th colspan="2">DOSES AND UNITS</th><th>CHANGES IN TREATMENTS</th><th colspan="3">TREATMENTS</th></tr>
<tr><th></th><th></th><th colspan="2">Dates of treatment prior to the appearance of the event</th><th>Last dose administered</th><th>Cumulative doses since the 1st adm.</th><th>(1) Reduction of doses
(2) Temporary interruption
(3) Final interruption</th><th>Disappearance
After stoppage of treatment
1 : Yes 2: No 3: NA</th><th>Reappearance
After reintroduction
1 : Yes 2: No 3: NA</th><th>Imputability:
1 : Excluded
2 : Doubtful
3 : Plausible
4 : Likely
5 : Very likely
6 : Cannot be concluded</th></tr>
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</table>

ANNEX 7:
Information form intended for the patient(1)

RANDOMIZED PHASE II / III STUDY COMPARING THE COCKTAIL OF ASSOCIATION FOLFIRINOX [OXALIPLATINE / IRINOTECAN / LV5FU] TO GEMCITABINE IN THE FIRST LINE OF CHEMOTHERAPY FOR PATIENTS WHO HAVE METASTATIC PANCREATIC CANCER

Sponsor: Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC), 101 rue de Tolbiac, 75654 PARIS CEDEX 13
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1. What is the objective of this study?

To Whom It May Concern,

Your doctor has informed you that you have pancreatic cancer that requires treatment. You are being offered the opportunity to participate in a study aimed at evaluating the efficacy of and tolerance to chemotherapy combining oxaliplatin, irinotecan and LV5FU (Folfirinox) compared to standard chemotherapy with gemcitabine.

2. How many people will take part in this study?

This Phase II national comparative study is being conducted by several teams of doctors in France. It should include 88 patients over a period of 2 years. Half of the patients will receive treatment with the Folfirinox cocktail, the other half with gemcitabine. The Phase III study will also be performed by the same doctors and will include, over the period of 3 years, **360 patients**.

3. What is the sequence of events for the study?

If you agree to take part in this study, you will need to be examined by your doctor and have a blood test, a thoracic, abdominal, pelvis CT scan, an electrocardiogram and complete a quality of life questionnaire. After these examinations have been carried out, and if there is no contraindication to either of the treatments, you will receive one of these treatments, the choice being decided by random drawing:

-Either treatment using **gemcitabine**, a potentially effective and well-tolerated chemotherapy drug. This is one of the reference treatments for your disease.

-Or a newer treatment known as **Folfirinox**, which uses drugs demonstrated to be effective against your disease, but not widely used in the current environment. This treatment cocktail combines three chemotherapy drugs:

- the cocktail of 5-fluorouracil (5FU) and folinic acid (LV5FU), a treatment recognized as being effective for your disease,
- Irinotecan (Campto®) and oxaliplatin (Eloxatin®), chemotherapy drugs marked to date only for treating cancers of the large intestines.

This combination (Folfirinox) has already been administered to patients with pancreatic cancer, and this treatment has shown encouraging efficacy.

The allocation of one of these options is determined by random drawing performed on a computer. The doctor and the patient have no influence on the allocation of treatments.

Treatment using Folfirinox:

Oxaliplatin is administered intravenously over a period of two hours by infusion on the first day of treatment. This will be followed by the simultaneous administration of folinic acid in a two-hour infusion and irinotecan in a 1.5-hour infusion, which begin immediately after the end of the oxaliplatin infusion.

The 5-FU is administered immediately after the end of the folinic acid infusion and will consist of an intravenous dose over 5 minutes followed by a continuous infusion over 46 hours.

This treatment will be repeated every 14 days and for a maximum duration of 6 months, i.e., 12 cycles

Treatment using Gemcitabine:

Gemcitabine is administered intravenously on the first day of treatment (D1) then every week on D8, D15, D22, D29, D36, D43. A course of treatment lasts 56 days.
This administration will then be resumed on D57 for 3 weeks out of 4, i.e., on D57, D64 and D71, and will be followed by a one-week break. This same schedule (3 weeks out of 4) will be continued for a period of 6 months.

Before each chemotherapy cycle, a biological assessment and a clinical examination will be carried out to verify that you are tolerating the treatment well. Every two weeks, prior to the consultation, your doctor will ask you to fill out a so-called "quality of life" questionnaire to find out how you are tolerating the treatments and how your daily life is going. It will take about ten minutes to answer. Filling out this questionnaire is very important to evaluate your quality of life throughout your disease.

You will be given an assessment at eight weeks. Your doctor will do a clinical examination, a biological assessment and a CT scan, then will ask you to complete the quality of life questionnaire.

A CT scan will be done every two months starting at the time of inclusion. Your participation in this study will not entail any additional constraints

Your doctor may decide at any time to suspend the treatment if this treatment is not effective on your disease, if the side effects of the treatment are considered too dangerous for you or if new information concerning the treatment suggests ineffectiveness or danger. You can also choose to withdraw from the trial at any time for any reason without there being any prejudice to the management of your disease. In both cases, the medical team that is in charge of your care will propose a therapy to you.

Folfirinox and gemcitabine can be performed on an outpatient basis.

4. How long does the patient participate in the study?

In any case, two months of chemotherapy treatment are initially planned. Then, depending on the results of an assessment carried out every two months and your tolerance to the treatment, you will be monitored for six months, then regularly for at least 2 years.

5. What are the expected benefits?

The goal of this study is to improve the treatment of your disease by evaluating the efficacy and tolerance of these two chemotherapies.

The main expected benefit is a total or partial reduction of the volume of your lesions and a reduction in the symptoms that you feel. The benefit could also be greater efficacy of the treatment (longer duration without progression of the disease) and/or less toxicity.

6. What are the possible risks?

Like all drugs of this type, the chemotherapy that you are going to receive may be responsible for adverse side effects. These are known by the doctors who will monitor you and who will give you either preventive treatments (anti-nausea, anti-vomiting) or curative treatments. Please report any effects to your doctor.

- Temporary nausea and vomiting will be alleviated by prescribing antiemetics;
- A risk of infection due to a drop in the number of white blood cells, an increased risk of hemorrhages, and therefore of the spontaneous appearance of bruises or hematomas, anemia due to a drop in the number of red blood cells as well as fatigue are fairly frequent events: They are monitored by regular blood tests;
- The appearance of a fever (temperature above 38 °C) may indicate a severe infection, especially if it is associated with diarrhea. A fever requires calling your doctor, who will prescribe a blood test.
- Muscle pain related to the administration of oxaliplatin may cause treatment to be stopped; in general, this neurotoxicity disappears in 6 to 8 months.
- With oxaliplatin, difficulty with fine perception may interfere with daily life (shirt buttoning, for example) and require a reduction in treatment.
- Abnormal fatigue is also possible
- During the irinotecan infusion, you may experience significant sweating, abdominal cramps, diarrhea, an increase in salivation or visual disturbances. When they appear, these symptoms are generally moderate and are effectively treated with an injection of atropine, if you do not present with a contraindication to this medication. If this injection was necessary, it will be repeated as a preventive measure during subsequent treatments
- During the oxaliplatin infusion, a feeling of spasm in the throat occurs very rarely. This is an illusion related to the throat anesthesia, but there is no risk of respiratory problems. This event is benign and disappears on its own. However, it will subsequently require extending the oxaliplatin infusion to 6 hours (instead of 2 hours).
- Diarrhea which, rarely, can be severe. If this is the case, you will need to take an anti-diarrheal treatment, Loperamide, to treat this diarrhea. In case you have severe and persistent diarrhea, your doctor will add antibiotics. If the diarrhea persists, the decision may be made to hospitalize you for a few days. A specific note of recommendations and a prescription for Loperamide and antibiotics will be given to you when you leave the hospital. You are asked to carefully read and follow these recommendations
- Hair loss may occur, and you may be prescribed a wig if you so desire. You can also use a cold cap, which limits the risk of hair loss.
- Tingling in the extremities when touching a cold object for a few days. You may also experience calf cramps for a day or two.
- A moderate fever and some muscle pain during the night following the gembitabine infusion.
- During treatment with Oxaliplatin and 5-FU, elevated liver enzymes numbers during monitoring blood tests are frequently observed. These elevations are generally mild and do not cause any symptoms. In a few cases, symptoms may be associated with these elevated liver enzymes numbers, consisting of jaundice, ascites (accumulation of fluid in the abdomen) or an enlargement of the liver and/or spleen. These liver abnormalities and symptoms may be related to your disease or, in rare cases, reflect a direct effect of the treatment on the liver tissue, which could change the

blood vessels in the liver (veno-occlusive disease). During the study, your liver function will be monitored regularly by blood tests and, if liver dysfunction or symptoms unrelated to your disease occur, additional tests will be offered to you.

- In case of anemia, your doctor may prescribe treatment with erythropoietin (Aranesp). Since an increased frequency of thromboembolic events has been observed in some patients treated with erythropoietin, particularly when the hemoglobin level is higher than 13 g/dl, increased monitoring of your blood count will be carried out. Furthermore, as with any growth factor, the risk of tumor growth cannot be completely ruled out with erythropoietins.

These side effects, of which we would like to give you a detailed description, are generally moderate and usually do not require stopping treatment. The treatment will be adapted to your individual susceptibility. It is imperative that you inform your doctor, who will assess their importance with you. In the event of significant toxicity, the doses of the molecules may have their dosage reduced, delayed or even eliminated.
You have the right to request that the treatment be stopped at any time if you so wish.

During chemotherapy, there is a significant risk of birth defects in the event of pregnancy. You or your partner must use effective contraception during the chemotherapy period and in the three months that follow. Before starting treatment, your doctor will ensure that you have the best method of contraception suited to your case.

It is important that you inform your doctor of any event that may occur between two chemotherapy treatments (cures), even if you think that this event is not related to the medication administered. In particular, you must inform your doctor of any diarrhea or fever.

7. What are the treatment alternatives?

Neither surgery nor radiotherapy can be offered to you, except in very specific cases. Radiation can sometimes help to better control pain and surgery is sometimes necessary to bypass the bile ducts and digestive tract in some cases. The usual treatment for your disease in your situation is chemotherapy by infusion. The alternative is to treat only your symptoms, without associating chemotherapy.

8. What are your rights as a participant in this study?

The sponsor of this trial, the *Fédération Nationale des Centres de Lutte Contre le Cancer* [National Federation of Cancer Control Centers] (FNCLCC), has taken all measures provided for by law for the protection of people participating in biomedical research (Huriet law of 12/20/1988, as amended). The sponsor has also underwritten biomedical research insurance, in accordance with current legislation, with Société Gerling France (111-113 rue de Longchamp, 75016 Paris) through the insurance brokerage firm Biomedic Insure (73, rue du général Weygand, 56037 Vannes, tel. 02 97 69 19 19).
The terms of this protocol were submitted for review to the *Comité Consultatif de Protection des Personnes dans la recherche Biomédicale* [Consultative Committee for the Protection of Persons in Biomedical Research] (CCPPRB) of Lorraine on April 8, 2004, whose mission is to verify whether the conditions required for your protection and respect for your rights have been respected. The CCPPRB of Lorraine issued a favorable opinion on May 18, 2004
In addition, per the provisions of the law of March 4, 2002, you will be informed by the investigator of the overall results of the trial.
This protocol has been examined by the *Comité de Patients de la Ligue Nationale Contre le Cancer* [Patients Committee of the French League Against Cancer].

Naturally, your medical file will naturally remain confidential and may be consulted only under the responsibility of the doctor in charge of your treatment, as well as by the health authorities and by persons duly mandated by the research organizer, subject to professional secrecy.

9. Who should you contact in case of questions or problems?

In case of problems or questions, you can contact the following people:

Your contacts in the study	Contact details of the patient's treating physician
(title, last name, first name, address and phone no.):	 ....

(1) all pages must be initialed by the investigator/co-investigator and the patient

10. What is the schedule for your treatment and examinations?

Treatment plan													
Date	**D1**	**D8**	**D15**	**D22**	**D29**	**D36**	**D43**	**D50**	**D57**	**D64**	**D71**	**D78**	**Dn**
Arm A: FOLFIRINOX	**C1**		**C2**		**C3**		**C4**		**C5**		**C6**		**Cn**
	oxaliplatin 85 mg/m² D1+ irinotecan 180 mg/m² D1+ folinic acid 400 mg/m² D1, 5-FU bolus 400 mg/m²D1, 5-FU continuous 2.4 g/m² over 46 hours D1/ D2 of each cycle								*Resumption of treatment according to the previous schedule, every 2 weeks*				
Arm B: gemcitabine	↑	↑	↑	↑	↑	↑	↑		↑	↑	↑		↑
	gemcitabine 1000 mg/m² every week for 7 weeks								*Resumption of gemcitabine 3 weeks out of 4*				

12 cycles planned for arm A = 6 months of treatment

ARM A Folfirinox monitoring plan									
Visit	**Inclusion analysis**	**Follow-up analysis**				**8-week analysis**	**Follow-up analysis after resumption**		
Visit No.	**V0**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**Vn**
Date	**D0**	**D1**	**D15**	**D29**	**D43**	**Around D50**	**D57**	**D71**	**Dn**
Signed informed consent	**X**								
Criteria for inclusion / non-inclusion	**X**								
Randomization	**X**								
Clinical examination									
Weight	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**
Body surface area	**X**								
Overall Status / WHO	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**
Concomitant treatments	**X**								
Toxicities (2)									
Tolerance evaluation			**X**	**X**	**X**	**X**	**X**	**X**	**X**
Biological examination (4)									
FBC, platelets	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
PT, KCT	**X**								
Electrolyte panel, Ca	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**
Serum total protein	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**
Total albumin, LDH	**X**								
Hepatic assessment	**X**		**X****	**X****	**X****	**X**	**Examination every two months**		
Serum creatine level	**X**	**X**	**X**	**X**	**X**	**X**	**Examination every two months**		
Blood sugar level	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**
CEA, Ca 19-9 *	**X**					**X**	**Examination every two months**		
Pregnancy test	**X**(1)								
Paraclinical assessment(3)									
Thoracic, abdominal, pelvis CT scan	**X**					**X**	**Scan examination every 2 months**		
ECG	**X**								
Quality of Life Questionnaire	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**

6 months of treatment expected for Arm B

ARM B GEMCITABINE monitoring plan													
Visit	**Inclusion analysis**	**Follow-up analysis**							**8-week analysis**	**Follow-up analysis after**			
Visit No.	**V0**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**Vn**
Date	**D0**	**D1**	**D8**	**D15**	**D22**	**D29**	**D36**	**D43**	**Around D50**	**D57**	**D64**	**D71**	**Dn**
Signed informed consent	**X**												
Criteria for inclusion / non-inclusion	**X**												
Randomization	**X**												
Clinical examination	**X**												
Weight	**X**	**X**		**X**		**X**		**X**	**X**	**X**		**X**	
Body surface area	**X**												
Overall Status / WHO	**X**	**X**		**X**		**X**		**X**	**X**	**X**		**X**	
Concomitant treatments	**X**												
Toxicities (2)													
Tolerance evaluation			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Biological examination (4)													
FBC, platelets	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
PT, KCT	**X**												
Electrolyte panel, Ca	**X**			**X**		**X**		**X**	**X**	**X**		**X**	
Serum total protein	**X**								**X**				
Total albumin, LDH	**X**												
Hepatic assessment	**X**			**X**		**X**		**X**	**X**	**Examination every two months**			
Serum creatine level	**X**			**X**		**X**		**X**	**X**	**Examination every two months**			
Blood sugar level	**X**			**X**		**X**		**X**	**X**	**X**		**X**	
CEA, Ca 19-9*	**X**								**X**	**Examination every two months**			
Pregnancy test	**X**(1)												
Paraclinical													
Thoracic, abdominal, pelvis CT scan	**X**								**X**	**Scan examination every 2 months**			
ECG	**X**												
Quality of Life Questionnaire	**X**			**X**		**X**		**X**	**X**	**X**		**X**	

**only the highest-performing marker will be measured later on; choose the marker that has the highest initial value compared to the normal value*

*** Hepatic assessment with total, free and conjugate bilirubin must be done at least once*

(1) a month for persons of childbearing age without effective contraceptive means

(2) Serious Adverse Events (SAE) are to be declared to the sponsor within 48 hours up to 30 days after the end of the last course of chemotherapy. Beyond that period, only those SAEs likely to be due to the research will be declared to the sponsor when no cause other than the research could be reasonably attributed thereto.

(3) The radiological assessment can be done during the 3 weeks prior to inclusion.

(4) The biological assessment must be done no later than one week prior to inclusion.

ANNEX 7:
Informed consent form for patient participation(1)

RANDOMIZED PHASE II STUDY COMPARING THE COCKTAIL OF [OXALIPLATINE / IRINOTECAN / LV5FU (FOLFIRINOX)] TO GEMCITABINE BY ITSELF IN FIRST LINE OF TREATMENT OF PATIENTS WHO HAVE METASTATIC PANCREATIC CANCER

I, the undersigned:

Last Name:…….First Name:…….

Address:……

EXPRESSLY CONSENT TO PARTICIPATING IN THIS RESEARCH UNDER THE CONDITIONS THAT HAVE BEEN SPECIFIED IN THE INFORMATION LITERATURE.

I have received and understood clearly the information that has been given to me by Dr. ……., who explained to me the objective, the sequence of events and how long this research will last, as well as the expected benefits and possible risks, specifying to me that I am free to accept or refuse.

My consent does not relieve the research organizers of their responsibilities. I retain all my rights guaranteed by law.

If I so desire, I will be free to stop my participation at any time. I will then inform Dr. …….. If I so wish, I will be offered another treatment.

Within the context of possible scientific publications, only information that does not mention my name or address may be used. The data concerning me will remain strictly confidential, and I authorize its consultation only by persons mandated by the research organizer or by a representative of the Health Authorities.

I also accept that the data recorded during this trial may be subject to computerized processing by the sponsor or on its behalf in accordance with the Data Protection Act of 1/6/1978, as amended by laws Nos. 94-548 of 7/1/1994 and No. 2002-303 of 3/4/2002. I have noted that the right of access (Articles 34 and 40, as amended) and rectification (Article 36), which the aforementioned texts give me, may be exercised at any time with Dr. ……. and that the data concerning me may be communicated to me or through a doctor of my choice.

_____	_____	_____
Name of patient or legal representative	Date	Signature
_____	_____	_____
Name of investigating physician or physician representing the patient (co-investigator):	Date	Signature

(1) *(all pages must be initialed, a co-signed copy must be given to the person taking part in the research)*

ANNEX 8:
Advice for using the EORTC QLQ-30 questionnaire for measuring the quality of life

1 – FILLING OUT THE QUESTIONNAIRE

- Provide a calm and comfortable environment for filling out the questionnaire.
- Give the questionnaire to the patient in person, remembering to bring an extra ballpoint pen (the patient may not have a pen with them).
- Make plans for assistance from a designated person (for example, nurse, assistant, clinical research technician, secretary) in case the patient needs explanations.
- Verbally explain instructions or questions if they seem unclear, making sure not to influence the answers. Show the patient how to circle (and not use a checkmark on) the responses.
- Sometimes put yourself in the patient's place by asking them the questions (elderly patients, tired patients or patients who have forgotten their glasses, etc.) and then mention it.
- When retrieving the questionnaire, make sure that any information not filled out is deliberate and not the result of an oversight.
- Note the reason why the patient may refuse to fill out the entirety of the questionnaire.

2 – TIME TO HAND OUT THE QUESTIONNAIRE

a – Prior to inclusion

- The patient must be aware of their situation prior to filling out the quality of life questionnaire.
- The doctor should have explained the goal of the questionnaire.
- Make sure that the questionnaire is filled out prior to randomization so that the outcome of randomization does not influence the quality of life results.
- The completion of the questionnaire will be a criterion for inclusion, since having the questionnaire prior to treatment will make it possible to detect a selection bias if subsequent follow-up is lacking (patients with a poor quality of life upon inclusion to whom we no longer dare to present a questionnaire because the QoL has deteriorated further).

b – Prior to each cure

- The questionnaire is considered acceptable if it is filled in on the day of treatment or within 3 days prior to treatment. Completion via telephone is not recommended.
- If the treatment is postponed, so will the filling out of the questionnaire.

c – At each handing out of the questionnaire

- The questionnaire is given to the patient, and it is preferred that it be filled in prior to the patient seeing the doctor, both to reduce biases linked to discussions with the doctor or those due to the results of the treatment, as well to allow the patient to discuss symptoms or areas of reduced quality of life with the doctor.
- It is not recommended that the questionnaire be taken home, as there will be no control over which day the questionnaire is actually filled in, and responses to the questionnaire will be influenced by family or friends.
- In case of severe symptoms described on the quality of life questionnaire, the person collecting the questionnaire can remind the patient to report problems to the doctor in charge of their chemotherapy.
- The questionnaire must be given at each scheduled treatment and also at the end of the study, even if the patient is not doing well (this is precisely when it is interesting to study the alterations in the quality of life, and it is important to try to correct them).

3 – INTERNAL ORGANIZATION OF EACH CENTER

- Appoint a person in each center to be in charge of handing out questionnaires and arrange for their replacement in the event of absence or holidays.
- Plan a schedule for handing out the questionnaires at the same time as randomization in the study, giving a duplicate to the patient and explaining it to them.
- Each center will keep a copy of the questionnaires prior to sending them along with the study files.
- Include a copy of the protocol summary in each file and make the complete protocol accessible in each care sector.

ANNEX 9:
EORTC QLQ-C30 (version 3.0)

We care about you and your health. Answer all the questions yourself by ***circling the number*** that best corresponds to your situation. There is no "right" or "wrong" answer. This information is strictly confidential.

	Not at all	A Bit	Somewhat	Very Much
1. Do you have difficulty performing strenuous physical tasks, such as carrying a heavy grocery bag or a suitcase?	1	2	3	4
2. Do you have difficulty taking a long walk?	1	2	3	4
3. Do you have difficulty taking a walk outside?	1	2	3	4
4. Are you required to stay in bed or in a chair during the day?	1	2	3	4
5. Do you need assistance with eating, dressing, bathing, or using the restroom?	1	2	3	4

DURING THE PAST WEEK:

	Not at all	A Bit	Somewhat	Very Much
6. Have you been hindered in performing your daily work or activities?	1	2	3	4
7. Have you been hindered in your leisure activities?	1	2	3	4
8. Have you experienced shortness of breath?	1	2	3	4
9. Have you been in pain?	1	2	3	4
10. Have you needed rest?	1	2	3	4
11. Have you had difficulty sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you experienced nausea (felt sick to your stomach)?	1	2	3	4
15. Have you thrown up?	1	2	3	4
16. Have you been constipated?	1	2	3	4
17. Have you had diarrhea?	1	2	3	4
18. Have you been feeling fatigued?	1	2	3	4

DURING THE PAST WEEK:

	Not at all	A Bit	Somewhat	Very Much
19. Have pain interfered with your daily activities?	1	2	3	4
20. Have you had difficulty concentrating on certain things, for example, reading the newspaper or watching TV?	1	2	3	4
21. Have you felt tense?	1	2	3	4
22. Have you felt worried?	1	2	3	4
23. Have you felt irritable?	1	2	3	4
24. Have you felt depressed?	1	2	3	4
25. Have you had difficulty remembering certain things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities (e.g., going out with friends, going to the movies, etc.)?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial problems?	1	2	3	4

For the next two questions, please answer by circling the number between 1 and 7 that best applies to your situation

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

1 2 3 4 5 6 7
Very bad **Excellent**

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

1 2 3 4 5 6 7
Very bad **Excellent**

ANNEX 10:
Recommendations for use of Filgrastim: (NEUPOGEN®)

ADMINISTRATION / DOSAGE:

The recommended dose of NEUPOGEN is 0.5 MU (5 µg)/kg/day. The first injection of NEUPOGEN must be administered no earlier than 24 hours after the completion of cytotoxic chemotherapy. NEUPOGEN must be administered daily either subcutaneously or via a 30-minute intravenous infusion, with the NEUPOGEN solution diluted in a 5% glucose solution (refer to the VIDAL dictionary for complete information on dilution).
Preference must be given to the subcutaneous route in the majority of cases.
Daily administration of NEUPOGEN must continue until the neutrophil nadir has been surpassed and the neutrophil count has returned to normal levels.

SPECIAL WARNINGS:

In cancer patients: Leukocytosis: Perform a leukocyte count at intervals.
Treatment must be discontinued if the leukocyte count exceeds $50x10^{9/l}$ after the expected nadir following chemotherapy or if the leukocyte count exceeds $70x10^{9/l}$ during stem cell collection.
Risks associated with intensive chemotherapy: No effect on thrombocytopenia or anemia due to cytotoxic chemotherapy. Monitor platelet count and hematocrit.
Other precautions: Caution in case of hereditary fructose intolerance.

INTERACTIONS*:

Administration not recommended within 24 hours prior to or following myelosuppressive chemotherapy.

CONTRAINDICATIONS:

NEUPOGEN must not be administered to patients with known hypersensitivity to the product or any of its components. NEUPOGEN must not be used to increase cytotoxic chemotherapy doses beyond established dosages. NEUPOGEN must not be administered to patients with severe congenital neutropenia (Kostmann syndrome) with cytogenetic abnormalities

PREGNANCY AND BREASTFEEDING*:

Safety not established.

ADVERSE EVENTS*:

In cancer patients: Most common: Bone pain, urinary disorders, mild to moderate biological changes, dose-dependent and reversible upon cessation of treatment (elevated gamma GT, elevated alkaline phosphatases, elevated LDH levels).
Rare cases: Transient drops in blood pressure, vascular disturbances, cutaneous vascularity, Sweet's syndrome (acute febrile dermatosis), flare-ups of rheumatoid arthritis, adult respiratory distress syndrome, and allergic reactions.

INCOMPATIBILITIES*: Saline solutions:

***For complete information, consult the VIDAL dictionary.**

ANNEX 11:
Recommendations for use of darbepoetin alfa (ARANESP®)

ADMINISTRATION / DOSAGE:

Aranesp® shall be administered subcutaneously at an initial dose of 6.75 µg/kg every 3 weeks in patients with anemia (e.g., hemoglobin level < 11 g/dL (6.8 mmol/L)). The target hemoglobin level to correct anemia and reduce transfusion needs is 12.0 g/dL or 7.5 mmol/L.

- If hemoglobin level exceeds 14.0 g/dL or 8.7 mmol/L, treatment must be interrupted (*see section 2 below*).
- If clinical response (fatigue, hemoglobin level) is unsatisfactory after 9 weeks (3 injections), Aranesp® must be discontinued.

Transfusion indications are at the clinician's discretion.

Do not forget to supplement with iron if serum ferritin is < 100 µg/L or if the transferrin saturation coefficient is < 20%.

Treatment with Aranesp® must continue for at least 4 weeks after chemotherapy ends, or until the hemoglobin level normalizes to a value greater than or equal to 12.0 g/dL or 7.5 mmol/L. A weekly full blood count (FBC) shall be performed.

MANAGEMENT:

1) **In case of Serious Adverse Events:** At any time during the study, any serious adverse event considered by the investigator to be related to treatment with Aranesp® shall entail immediate decision to discontinue treatment. Following this, regular follow-up of the patient shall be ensured until the event resolves or stabilizes.

It is recommended that Aranesp® not be administered if the hemoglobin level is > 11 g/dL. It is essential to ensure that this level does not exceed 13 g/dL. If hemoglobin increases by more than 2 g/dL in four weeks, reduce the dose by 25% to 50%.

ANNEX 12:
List of Expected Serious Adverse Events (SAEs)

Excerpt from the SPC of Oxaliplatin - ELOXATINE®

CR/ADVERSE EVENTS
The adverse events reported during the clinical development of oxaliplatin in the treatment of metastatic colorectal cancer were analyzed in a population of 244 patients treated with monotherapy and nearly 1500 patients treated in combination with 5-fluorouracil.

- **Hematopoietic System:**

Oxaliplatin administered as monotherapy (130 mg/m² every 3 weeks) results in minimal hematological toxicity of grades 3 and 4.

Oxaliplatin alone	All grades	Grade 3	Grade 4
Anemia (% of patients)	64	3	< 1
Neutropenia (% of patients)	15	2	< 1
Thrombocytopenia (% of patients)	41	2	< 1

When oxaliplatin is used in combination with 5-fluorouracil and folinic acid, the incidence of neutropenia and thrombocytopenia is higher than that observed with the 5-fluorouracil/folinic acid combination alone.

Oxaliplatin combined with 5-fluorouracil	85 mg/m² every 2 weeks		
	All grades	Grade 3	Grade 4
Anemia (% of patients)	83	4	< 1
Neutropenia (% of patients)	66	25	13
Thrombocytopenia (% of patients)	76	3	< 1

- **Digestive System:**

In monotherapy, oxaliplatin (130 mg/m² every 3 weeks) may cause anorexia, nausea, vomiting, diarrhea, and abdominal pain, which are not severe in the majority of cases.

Oxaliplatin alone	All grades	Grade 3	Grade 4
Nausea, vomiting (% of patients)	69	12	2
Diarrhoea (% of patients)	41	4	< 1
Mucositis (% of patients)	4	< 1	< 1
Hepatic abnormalities (% of patients)	46	10	2

A preventive and/or therapeutic treatment with strong antiemetic agents is recommended. When oxaliplatin is combined with 5-fluorouracil (with or without folinic acid), the frequency and severity of diarrhea and mucositis are significantly increased compared to that observed with 5-fluorouracil alone.
Rare cases of colitis, including Clostridium difficile-associated diarrhea, have been reported. Severe diarrhea and/or vomiting may cause dehydration, paralytic ileus, intestinal obstruction, hypokalemia, metabolic acidosis, and renal function impairment, particularly when oxaliplatin is combined with 5-fluorouracil (see Warnings/Precautions)

Oxaliplatin combined with 5-fluorouracil	85 mg/m² every 2 weeks		
	All grades	Grade 3	Grade 4
Nausea, vomiting (% of patients)	71	11	1
Diarrhoea (% of patients)	58	7	3
Mucositis (% of patients)	42	7	1

Liver enzyme elevations of grades 1 and 2 are common during oxaliplatin treatment. In randomized studies comparing the combination of 5-fluorouracil/folinic acid with the combination of 5-fluorouracil/folinic acid/oxaliplatin, the incidence of liver enzyme elevations of grades 3 and 4 is comparable in both groups.

- **Nervous System:**

The limiting toxicity of oxaliplatin is neurological. It mainly manifests as peripheral sensory neuropathy, characterized by dysesthesias and/or paresthesias in the extremities, with or without cramps, often triggered by cold. These symptoms occur in 85% to 95% of treated patients. The duration of these symptoms, typically resolving between treatment cycles, increases with repeated cycles.

The occurrence of pain and/or functional discomfort may require dose adjustments or even discontinuation of treatment, depending on the duration of symptoms (see Warnings/Precautions for Use).
This functional discomfort, which includes difficulties performing fine motor tasks, is a possible consequence of sensory nerve damage. The risk of functional discomfort with a cumulative dose of approximately 800 mg/m² (i.e., 10 cycles) is 15% or less. Neurological symptoms most often improve upon discontinuation of treatment.
Acute sensory neurosensory events have been reported (see Preclinical Safety). They start within hours of administration and are often triggered by cold exposure. They are characterized by transient paresthesias, dysesthesias or hypoaesthesias, or even by an acute pharyngolaryngeal dysesthesia syndrome. This acute syndrome, with an incidence estimated between 1% and 2%, is characterized by subjective sensations of dysphagia or dyspnea without objective signs of respiratory distress (no cyanosis or hypoxia), or by laryngospasm or bronchospasm (without stridor or wheezing); jaw contracture, tongue dysesthesia, dysarthria, and chest tightness have also been observed.
Although antihistamines and bronchodilators have been administered in these situations, the symptoms are rapidly reversible, even without treatment. Prolonging the infusion time in subsequent cycles helps reduce the incidence of this syndrome (see Warnings/Precautions of Use).
Other neurological symptoms, such as dysarthria, disappearance of osteotendinous reflexes, and Lhermitte's sign, have been reported during oxaliplatin treatment. Isolated cases of optic neuritis have been reported.

- **Allergic Reactions:**

Infrequent anaphylactic reactions (in monotherapy) or frequent reactions (in combination with 5-fluorouracil ± folinic acid) have been reported, including cases of bronchospasm, angioedema, hypotension, and anaphylactic shock.

Frequent allergic reactions such as skin rashes (especially urticaria), conjunctivitis, and rhinitis have been reported.

- **Other Effects:**

Clinical ototoxicity occurred in less than 1% of patients treated with oxaliplatin. Rare cases of deafness have been reported.
Renal function abnormalities have been reported in approximately 3% of treated patients, grade 3 and 4 abnormalities in less than 1% of patients.
In clinical studies and since its market launch, no significant ventricular arrhythmia has been reported with oxaliplatin administration.
Very frequent cases of fever have been reported: either isolated immunological fevers or fever of infectious origin (with or without neutropenia).
Rare cases of immunoallergic thrombocytopenia and immunoallergic hemolytic anemia have been reported.
Rare cases of acute interstitial pneumonia and pulmonary fibrosis have been reported (see Warnings/Precautions).
Moderate alopecia has been reported in 2% of patients treated with oxaliplatin alone; the combination of oxaliplatin and 5-fluorouracil does not increase the incidence of alopecia observed in treatments with 5-fluorouracil alone.
Extravasation may cause localized pain and inflammation, which can be severe and lead to complications, particularly when oxaliplatin is infused via a peripheral vein (see Warnings/Precautions).
A transient decrease in visual acuity has been reported in less than 0.1% of patients following oxaliplatin administration.
Dysarthria has been rarely reported (see above: nervous system).

Excerpt from the SPC of Irinotecan - CAMPTO®

CR/ADVERSE EVENTS

The following adverse events, possibly or probably related to the administration of Campto, were analyzed in a population of 765 patients at the recommended dose of 350 mg/m^2 in monotherapy, and 145 patients treated with Campto in combination with 5-FU/FA every 2 weeks at the recommended dose of 180 mg/m^2.

Gastrointestinal Events:

- Delayed Diarrhea:

  Delayed diarrhea (occurring more than 24 hours after Campto administration) is a dose-limiting toxicity of Campto.

  - In monotherapy: Severe diarrhea is observed in 20% of patients who followed the diarrhea management recommendations. Severe diarrhea is found in 14% of evaluable cycles. The median time to the first liquid stool is 5 days after the Campto infusion.
  - In combination: Severe diarrhea is observed in 13.1% of patients who followed the diarrhea management recommendation Severe diarrhea is found in 3.9% of evaluable cycles.

  Rare cases of pseudomembranous colitis have been reported, including one case with bacteriological documentation (Clostridium difficile).

- Nausea and Vomiting:

  - In monotherapy: Severe nausea and vomiting are observed in approximately 10% of patients who received antiemetic treatment.
  - In combination: A lower incidence of severe nausea and vomiting is observed (2.1% and 2.8% of patients, respectively).

- Dehydration: Episodes of dehydration, typically associated with diarrhea and/or vomiting, have been reported. Rare cases of renal failure, hypotension, or cardiovascular collapse have been observed in patients who experienced dehydration associated with diarrhea and/or vomiting.

• Other Gastrointestinal Events: Constipation related to Campto and/or loperamide has been observed in monotherapy in less than 10% of patients and, in combination, in 3.4% of treated patients. Rare cases of intestinal obstruction, ileus, or gastrointestinal bleeding, and rare cases of colitis, including typhlitis, ischemic colitis, and ulcerative colitis, have been reported. Rare cases of intestinal perforations have been reported. Other mild effects, including anorexia, abdominal pain, and stomatitis, have also been observed.

Hematology:

Neutropenia is a dose-limiting toxicity. Neutropenia was reversible and non-cumulative; the median time to nadir was 8 days, whether in monotherapy or in combination.

• In monotherapy: Neutropenia is observed in 78.7% of patients and is severe (neutrophil count < 500/mm³) in 22.6% of cases. Among evaluable cycles, 18% complicate with neutropenia < 1000/mm³, of which 7.6% have neutropenia < 500/mm³. Full recovery is generally achieved by day 22. Fever accompanied by severe neutropenia is reported in 6.2% of patients and in 1.7% of cycles. Infectious episodes occurred in approximately 10.3% of patients (2.5% of cycles), were associated with severe neutropenia in approximately 5.3% of patients (1.1% of cycles), and resulted in 2 deaths. Anemia was reported in approximately 58.7% of patients (8% with hemoglobin < 8 g/dL and 0.9% with hemoglobin < 6.5 g/dL). Thrombocytopenia (< 100,000/mm³) was observed in 7.4% of patients and 1.8% of cycles, with 0.9% of patients having platelets ≤ 50,000/mm³, or 0.2% of cycles. Almost all patients normalized their platelet count by day 22.

• In combination: Neutropenia is observed in 82.5% of patients and is severe (neutrophil count < 500/mm³) in 9.8% of cases. Among evaluable cycles, 67.3% complicate with neutropenia < 1000/mm³, of which 2.7% have neutropenia < 500/mm³. Full recovery is generally achieved in 7 to 8 days. Fever accompanied by severe neutropenia is reported in 3.4% of patients and in 0.9% of cycles. Infectious episodes occurred in approximately 2% of patients (0.5% of cycles), were associated with severe neutropenia in approximately 2.1% of patients (0.5% of cycles) and resulted in 1 deaths. Anemia is reported in approximately 97.2% of patients (2.1% with hemoglobin < 8 g/dL). Thrombocytopenia (< 100,000/mm^3) was observed in 32.6% of patients and 21.8% of cycles. No severe thrombocytopenia (< 50,000/mm^3) was observed.

A case of peripheral thrombocytopenia with anti-platelet antibodies has been reported in clinical experience following market approval.

Infection:

Rare cases of renal failure, hypotension, or cardiovascular collapse have been observed in patients with severe systemic infection.

General adverse events and injection site reactions:

• Acute cholinergic syndrome: An acute, transient, and severe cholinergic syndrome is observed in 9% of patients treated with monotherapy and 1.4% of patients treated with combination therapy. The main symptoms are defined by early diarrhea and a set of symptoms such as abdominal cramps, conjunctivitis, rhinitis, hypotension, vasodilation, excessive sweating, chills, malaise, dizziness, visual disturbances, miosis, tearing, and hypersalivation occurring during or within 24 hours following the administration of Campto. The symptoms resolve with atropine administration (see Warnings/Precautions). Severe asthenia has been observed in less than 10% of patients treated with monotherapy and in 6.2% of patients treated with combination therapy. Causality to Campto is not clearly established. Isolated fever not associated with infection or severe neutropenia occurred in 12% of patients treated with monotherapy and 6.2% of patients treated with combination therapy. Moderate injection site reactions have been infrequently reported.

• Cardiovascular disorders: Rare cases of hypertension during or following infusion have been reported.

• Respiratory disorders: Rare cases of interstitial pneumonia and pneumonia with pulmonary infiltrates have been observed. Early effects such as dyspnea have been reported.
• Skin and subcutaneous disorders: Alopecia is very common and reversible. Moderate and infrequent skin reactions have been reported.
• Immune system disorders: Moderate and infrequent allergic reactions and rare cases of anaphylactic/anaphylactoid-type reactions have been reported.
• Musculoskeletal disorders: Early effects such as muscle contraction or cramps and paresthesias have been reported.

Biological Examinations: In monotherapy, a minor to moderate transient increase in serum levels of transaminases, alkaline phosphatases, or bilirubin was observed in 9.2%, 8.1%, and 1.8% of patients, respectively, in the absence of progression of liver metastases. A minor to moderate transient increase in serum creatinine levels was observed in 7.3% of patients. In combination therapy, a transient increase (grades 1 and 2) in serum ALT, AST, alkaline phosphatases, or bilirubin was observed in 15%, 11%, 11%, and 10% of patients, respectively, in the absence of progression of liver metastases. Grade 3 transient increases were observed in 0%, 0%, 0%, and 1% of patients, respectively. No grade 4 was observed. In very rare cases, an increase in serum amylase and/or lipase has been reported. Rare cases of hypokalemia, mainly related to diarrhea and vomiting, have been reported. *Nervous system disorders:* Very rare cases of transient language disorders have been reported during Campto infusions.

Excerpt from the SPC of 5-Fluorouracil:

CR/ADVERSE EVENTS

Stomatitis, Mucosal iInflammation, Diarrhea, Anorexia, Nausea, Vomiting, Digestive haemorrhage (Exceptional), Skin staining, Alopecia, Dermatitis, Rash, Urticaria, Photosensitization, Precordial pain, Electrocardiogram(abnormality), Myocardial infarction (Exceptional), Leukopenia, Thrombocytopenia, Anaemia (Rare), Ataxia, Tearing

Excerpt from the SPC of Folinic Acid

CR/ADVERSE EVENTS

These are dose-dependent and depend on the administration regimen of 5-fluorouracil:

Diarrhea: In elderly patients, risk of dehydration (see Warnings/Precautions); mucositis, stomatitis (see Warnings/Precautions of Use); skin reactions: dry skin, erythema; conjunctivitis, tearing; moderate hematological toxicity.

Excerpt from the SPC of Gemcitabine – GEMZAR®

CR/ADVERSE EVENTS

- Hematological: Gemcitabine can induce bone marrow suppression, leading to anemia, leukopenia, and thrombocytopenia. Myelosuppression is generally mild, with a more pronounced effect on the granulocyte lineage. Thrombocytosis is another frequently reported event.

- Hepatic: Increases in hepatic transaminases are observed. These are usually mild, transient, and rarely require discontinuation of treatment. Caution is advised, however, in patients with impaired liver function.

- Esophageal-Gastrointestinal: Nausea, sometimes accompanied by vomiting. These side effects require therapeutic measures in approximately 20% of cases but rarely necessitate dose reduction and are easily treated with conventional antiemetics. Diarrhea, oral toxicity in the form of mucositis.

- Pulmonary: Within hours following the administration of gemcitabine, patients may experience dyspnea, which is generally mild and short-lived. It rarely requires a dose reduction and usually resolves without specific treatment.

The mechanism is unknown, and its relationship with gemcitabine is unclear. Cases of pulmonary edema, interstitial pneumonia, and adult respiratory distress syndrome (ARDS) of unknown etiology have been reported during treatment with gemcitabine. Upon occurrence, discontinuation of gemcitabine should be considered.

- Renal: Moderate proteinuria and hematuria occur in nearly half of the patients but are rarely clinically significant; they are typically not associated with changes in serum creatinine or blood urea levels. However, some cases of renal insufficiency of unclear etiology have been reported. No cumulative renal toxicity has been observed (see Warnings/Precautions). Clinical manifestations compatible with a hemolytic-uremic syndrome have been reported in patients receiving gemcitabine. Treatment with gemcitabine should be interrupted at the first signs of microangiopathic hemolytic anemia, such as a sudden drop in hemoglobin with concomitant thrombocytopenia, elevated serum bilirubin, serum creatinine, blood urea, or LDH. Renal insufficiency may not be reversible, even after discontinuation of treatment, and dialysis may be required.

- Allergic: Rashes may occur and be accompanied by pruritus. Rashes are usually mild, do not require dose reduction, and respond to local treatment. Scaling, vesiculation, and ulceration are occasionally reported side effects. Bronchospasm has sometimes been reported. This bronchospasm is usually of moderate and transient intensity, but it may require parenteral treatment. Gemcitabine must not be administered to patients with known hypersensitivity to the product. Rare cases of anaphylactic reactions have been reported.

- Cardiac: Cases of myocardial infarction, congestive heart failure, and arrhythmia have been observed. A few cases of hypotension have been reported.

- Skin: Severe cutaneous-muscular manifestations such as dermatopolymyositis at the previously irradiated site have been reported after the successive administration of radiotherapy and gemcitabine.

- Other: A rarely severe flu-like syndrome may occur. It is generally short-lived and rarely requires a dose reduction. Fever, headaches, back pain, chills, myalgia, asthenia, and anorexia are the most commonly reported symptoms. Similarly, cough, rhinitis, malaise, sweating, and insomnia are frequently reported. Fever and asthenia are also reported as isolated symptoms. The mechanism underlying this toxicity is unknown. Paracetamol may alleviate symptoms.
Peripheral edema, very rarely facial edema. Peripheral edema is usually mild and rarely requires dose reduction but can be painful; it is generally reversible after the discontinuation of gemcitabine. The mechanism underlying this toxicity is unknown. There is no association with signs of heart failure, liver failure, or renal failure. The following side effects are also commonly reported: alopecia (usually minimal), drowsiness.

[logo : CRLC
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Paul Lamarque
Regional Cancer Treatment Center
Healthcare Facility M A S Certified in 2007
Smoke-free facility, member of the Smoke-free Hospitals network.]

Biostatistics Unit
CTD labeled INCa

Statistical Analysis Plan (Phase III)

PROTOCOL AGREEMENT 11/0402

EudraCT No.: 2004-001985-42

RANDOMIZED PHASE II/III STUDY COMPARING THE FOLFIRINOX COMBINATION [OXALIPLATIN / IRINOTECAN / LV5FU] WITH GEMCITABINE AS FIRST-LINE CHEMOTHERAPY IN PATIENTS WITH METASTATIC PANCREATIC CANCER

Version 1, 07/03/2009

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AGREEMENT 11/0402

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Version	1
Date	Friday, July 10, 2009

Signatures Page

I have read this statistical analysis plan and confirm that all study objectives as outlined in the protocol are covered.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviations	Definition
EI	Intercurrent Events (AE = Adverse Event)
ALAT	Alanine Aminotransferase
PAL	Alkaline Phosphatase
ASAT	Aspartate Aminotransferase
BSA / SC	Body Surface Area
SC / BSA	Body Surface Area
CRF	Case Report Form
DI	Dose Intensity
DMC	Data Monitoring Committee
ECG	Electrocardiogram
EORTC	European Organization for Research and Treatment of Cancer
ICH	International Conference on Harmonization
iDMC	Independent Data Monitoring Committee
ITT	Intention-to-Treat
NCI-CTC	National Cancer Institute - Common Toxicity Criteria
QLQ-C30	Quality of Life Questionnaire – C30
QLQ-PAN24	Quality of Life Questionnaire – PAN24
RDI	Relative Dose Intensity
SAP	Statistical Analysis Plan

1 RATIONALE

The Statistical Analysis Plan (SAP) describes the statistical analyses to be conducted for the ACCORD 11/0402-Prodige 4 study, specifically for the Phase III portion.
A brief description of the study planning will be provided, followed by details of the analysis populations and the statistical methods used. The tables and listings to be produced will also be detailed
This SAP was drafted based on the following documents:

- The original protocol, including all amendments (version 9).
- International Conference on Harmonization (ICH) guideline E9 (Statistical Principles for Clinical Trials).

2 STUDY OBJECTIVES

The primary objective of the study is to evaluate the efficacy in terms of overall survival of the combination of oxaliplatin, irinotecan, 5-fluorouracil, and folinic acid (Folfirinox – Arm A) in the treatment of metastatic pancreatic cancer compared to the standard treatment with gemcitabine (Arm B).

Phase III:

Primary Objective:

- Compare the overall survival between the two treatment regimens, Folfirinox combination (Arm A) vs. the standard gemcitabine treatment (Arm B).

Secondary Objectives:

- Compare progression-free survival between the two arms.
- Compare quality of life between the two arms.
- Compare response rates.
- Compare treatment toxicity.
- Assess quality of life using the EORTC QLQ-C30 and PAN24 questionnaires.

3 STUDY METHODOLOGY

3.1 Description

This trial is a Phase II/III, multicenter, randomized study.
Eighty-eight patients with metastatic pancreatic cancer will be randomized in the Phase II study. At the end of Phase II, if the decision to proceed with Phase III is made, an additional 272 patients will be randomized in Phase III to reach a total of 360 patients.

Patients shall be randomized 1:1 according to the following two treatment arms:

- **Arm A: Folfirinox** (oxaliplatin (Eloxatine®) 85 mg/m² on Day 1 over 2 hours, followed by irinotecan (Campto®) 180 mg/m² on Day 1 over 90 minutes + folinic acid 400 mg/m² on Day 1 over 2 hours (during the irinotecan infusion) + 5-FU bolus 400 mg/m² on Day 1 followed by continuous 5-FU infusion of 2.4 g/m² over 46 hours, with 1.2 g/m² on Day 1 and 1.2 g/m² on Day 2).

- **Arm B: Gemcitabine** (1000 mg/m² over 30 minutes via strict intravenous infusion, on Days 1, 8, 15, 22, 29, 36, 43; Gemcitabine resumes on Day 57, every 3 weeks on 4-week cycles (Days 57, 64, 71 followed by one week off)).

3.2 Study Design

3.2.1 Study Duration

Patients in Arm A (Folfirinox) shall be treated until progression, with a maximum of 12 cycles recommended.

Patients in Arm B (Gemcitabine) shall be treated until progression, with a maximum of 6 months recommended.

Beyond the protocol treatment period, the patient's management, whether medicinal or otherwise, is left to the investigator's discretion.

In case of progression, the treatment approach shall also be at the investigator's discretion.

All patients shall be followed up until death.

3.2.2 Treatment

- **Arm A: Folfirinox**
  - oxaliplatin (Eloxatine®)85 mg/m² on Day 1 over 2 hours,
  - irinotecan (Campto®) 180 mg/m² on Day 1 over 90 minutes,
  - folinic acid 400 mg/m², Day 1 over 2 hours (during irinotecan infusion),
  - 5-FU bolus 400 mg/m² Day 1 followed by continuous 5-FU infusion 2.4 g/m² over 46 hours, with 1.2 g/m² on Day 1 and 1.2 g/m² on Day 2.

- **Arm B: Gemcitabine**
  - gemcitabine (1000 mg/m² over 30 minutes via strict intravenous infusion, on Days 1, 8, 15, 22, 29, 36, 43; Resumption of Gemcitabine on Day 57, every 3 weeks on 4-week cycles (Days 57, 64, 71 followed by one week off)).

3.2.3 Treatment Allocation Method

Centralized randomization (via Oracle Forms by Euraxi Pharma) was performed using a minimization method according to the following stratification factors:

- WHO performance status (0 vs 1),
- location (head vs other),
- site (n modalities),

Patients shall be randomized at a 1:1 ratio into the two treatment arms: Arm A: Folfirinox
Arm B: Gemcitabine.

3.3 Data Monitoring Committee (DMC):

An independent DMC (iDMC) has been established to monitor inclusion progress, treatment tolerability, and treatment efficacy. The iDMC consists of 2 medical oncologists, 2 radiotherapists, and a statistician not participating in the study.

The iDMC shall be consulted at each step of the planned interim analyses.

3.4 Phase III Decision

At the end of Phase II, the decision was made to continue with randomized Phase III inclusions, with the primary objective of evaluating overall survival.

3.5 Interim Analysis During Phase III

An interim efficacy analysis shall be conducted when 2/3 of the events (deaths) have been observed, i.e., **167 events**. To maintain a global risk of 5%, this interim analysis shall be considered significant only if the p-value is less than or equal to 0.001 and $\mathbf{p \leq 0.049}$ in the final analysis.

The Data Monitoring Committee (iDMC) may propose early termination of the trial if it deems necessary and if the available data from the trial or other sources is sufficiently convincing to influence the therapeutic practices of most physicians.

4 DETERMINATION OF THE NUMBER OF SUBJECTS REQUIRED

4.1 Phase II

A total of 88 patients were to be enrolled in Phase II (44 per arm). In reality, 97 patients were included and shall be used in the Phase III analysis.

4.2 Phase III

To detect a difference in median survival of 3 months (from 7 to 10 months median), corresponding to a relative risk of 0.70, **360 patients** will need to be included to maintain a global alpha risk of 5%, accepting a beta risk of 20% (study power = 80%).
This power will be achieved when **250 events** have been observed (calculated using the East 5 software).

Since 97 patients were included during Phase II, 263 additional patients will need to be included in Phase III to reach the required 360 patients.

5 PARAMETERS OF EFFICACY AND TOLERABILITY

5.1 Primary Endpoint

The primary endpoint is **overall survival** calculated from the date of randomization and the occurrence of death. Living patients at the latest follow-up shall be excluded.

5.2 Secondary Endpoints

The secondary endpoints are as follows:

- **Progression-free survival,** defined as the time between randomization and the first evidence of documented progression, death, or the latest follow-up date. Living patients without relapse shall be excluded.
- **Response rate** (according to RECIST criteria): The best recorded response between the start of treatment and disease progression or the latest evaluation (best overall response). The response is defined according to RECIST criteria. All objective responses must be confirmed 4 weeks after their observation by a new examination. An independent committee of 2 expert radiologists shall review all radiological tumor assessments to confirm the recorded responses.
- **Duration of overall response**, calculated from the date the criteria for partial or complete response are first met to the date of documented first progression.
- **Toxicity incidence** (according to NCI version 3.0 toxicity scale),
- **Quality of life assessment** using the EORTC QLQ-C30 questionnaire (version 3) and the specific EORTC-PAN24 module.

5.3 Tolerability Parameters

Tolerability parameters shall include all information collected in the observation booklet according to the CTC-NCI v3.0 scale, after reconciliation with the sponsor's pharmacovigilance data.

6 DEFINITION OF POPULATIONS

ITT (Intention-to-Treat) Population: All patients randomized into the treatment arm (intention to treat).

Evaluable for Tolerability Population: All randomized patients who have received at least one course or injection of treatment.

Eligible population: All randomized patients who have received at least one dose of treatment and who have not violated inclusion or exclusion criteria.

Evaluable for Tumor Response Population:
To be defined, see Phase II SAP.

An ITT analysis shall be performed on all endpoints.

7 STATISTICAL ANALYSES

7.1 Statistical Methods

7.1.1 Descriptive Statistics

Quantitative variables shall be described by the number of observations, the median, the minimum, and the maximum. Unless otherwise specified, the median shall be presented with one decimal point in addition to the measured value.
Qualitative variables shall be described by the number of observations (N) and the frequency (%) with the percentage relative to the total population. Missing categories shall be added to report all data. Percentages shall be presented with one decimal point.
Descriptive analyses shall be summarized by treatment arm and globally only for baseline characteristics.

The p-value shall be presented with 3 decimal places unless otherwise specified.
Tables and listings shall be generated by STATA v10.0.

7.1.2 Qualitative Variables

The Chi-square test shall be used to compare proportions (or Fisher's exact test if expected frequencies <5).
Ninety-five percent confidence intervals for proportions shall be calculated using the exact binomial method.

7.1.3 Survival Data

Survival data corresponds to the observation of the time until a particular event occurs (e.g., time to death).

The Kaplan-Meier method shall be used to analyze survival data and to estimate median survival times. Kaplan-Meier survival curves shall be presented. The 95% confidence interval for the median survival shall be calculated using the Brookmeyer and Crowley method (1982).
Survival distributions shall be compared using the log-rank test.

HRs and their 95% confidence intervals shall be estimated using a Cox proportional hazards model, adjusted for stratification factors used for randomization (WHO, location, center). The Cox model shall be used to compare survival distributions after adjusting for potential prognostic factors.

The validity of proportional hazards shall be assessed graphically and/or tested for time-dependent covariates. If non-proportionality of risks is found, survival distributions shall be compared using the modified Kolmogorov-Smirnov test, and this shall be considered as support for comparisons planned by the log-rank test.

7.2 Definitions and Conventions

7.2.1 Definitions

Age shall be calculated as follows:
Age = int((date at screening visit – date of birth) / 365.25)

Body surface area shall be calculated according to the Dubois and Dubois formula [2]
BSA/SC = (weight in kg) $^{0.425}$ * (height in m)$^{0.725}$ * 0.20247

Body Mass Index shall be calculated as follows:
BMI = weight / (height in m)^2
Then **BMI_cl** according to 4 categories: Lean <18.5 / normal<25 / overweight<30 / obese≥30

Cycle Day 1:
Day 1 of the cycle is defined as the date of the 1st administration of the cycle.

Treatment Discontinuation:
Patients are considered under treatment for the duration of the treatment and for the 30 days following treatment cessation.
Treatment discontinuation is defined as the last day the subject receives study treatment.

7.2.2 Conventions

Time-to-event shall be calculated from the date of randomization.
For any calculation of time or duration between two dates, the following convention shall be applied: **[later date] – [earlier date] + 1 day**.
To convert a number of days into a year or month, the following convention shall be applied: **1 year = 365.25 days**; **1 month = 30.4375 days**.

7.2.3 Missing Data

Unless otherwise specified, missing values shall not be estimated.

7.2.4 Missing or Incomplete Dates

From EURAXI, convention for the first analysis for the iDMC in December 2008:
If the day of a date is missing, the central day of the month (15th) shall be assigned.

7.3 Patient Characteristics

On the ITT Population

7.3.1 Disposition of Patients

The following shall be summarized by treatment arm:

- Disposition of patients: ITT population (randomized subjects), evaluable for tolerability population, eligible population, evaluable for tumor response population.
- Administration of Treatments and Reason for Discontinuation

The following listings shall be created as support:

- Subjects excluded from the evaluable for tolerability population (subjects not treated)

- Subjects not eligible
- Subjects not evaluable for tumor response

7.3.2 Protocol Deviations

Following the iDMC of December 2008, the distinction between major and minor deviations is unnecessary as all analyses shall be performed in ITT.

7.3.3 Randomization Factors

The factors recorded at the time of randomization shall be described:

- Sex: male/female: frequency and %
- Age (years): median and range
- WHO performance status: frequency and %
- Tumor location: frequency and %

7.3.4 Demographic Characteristics

Demographic characteristics shall be summarized according to randomization information and inclusion assessment.

- Sex: male/female: frequency and %
- Age (years): median and range
- WHO performance status: frequency and %
- Weight (kg): median and range
- Height (cm): median and range
- Body Surface Area (m^2): median and range
- BMI (kg/m^2) shall be calculated: median and range

The groups shall be compared to evaluate initial comparability based on these characteristics.

7.3.5 Physical Examinations and QLQ-C30

Exams performed at inclusion shall be described:

- Thoraco-abdominopelvic CT scan: Time from randomization, frequency and % of normal/abnormal result,
- ECG: Time from randomization, frequency and % of normal/abnormal results,
- Pregnancy test in women: Time from randomization, frequency and % of positive/negative results.
- Quality of Life (QLQ-C30): Initial scores for the 8 dimensions evaluated / median and range.

7.3.6 Disease Characteristics

The groups shall be compared to evaluate initial comparability based on these characteristics.

7.3.6.1 Primary Tumor

Characteristics of the primary tumor shall be summarized according to the inclusion assessment (CRF p3).

- Time from diagnosis to randomization
- Type of diagnosis, differentiation
- Time from randomization to tumor evaluation

- Type of exam, pTNM classification, cTNM classification
- Primary tumor location
- Maximum tumor size
- Any prior treatments (including time from randomization)

7.3.6.2 Metastatic Tumor

Characteristics of the metastatic tumor shall be summarized according to the inclusion assessment (CRF p3).

- Time from diagnosis to randomization
- Type of diagnosis, differentiation
- Time from randomization to tumor evaluation
- Type of exam, pTNM classification, cTNM classification
- Any prior treatments (including time from randomization)
- Tumor markers (CA19-9, ACE)
- Number of metastatic sites
- Nature of metastatic sites
- Number of measurable and non-measurable lesions and sites

7.3.7 Initial Biology and Tumor Markers

The following initial biological results shall be identified as "Not done" / "Normal" / "Abnormal" and described as such:

- Hematological Assessment: Hemoglobin, neutrophils/granulocytes, platelets, PT, and other hematological markers.
- Biochemical Assessment: Calcium, glucose, albumin, protein levels, other
- Hepatic Assessment: Total/free bilirubin, LDH, alkaline phosphatase (ALP), ALT (SGPT), AST (SGOT), gamma GT, other
- Renal Assessment: Serum creatinine, other

7.4 Study Treatments

7.4.1 Arm A: FOLFIRINOX

For each drug, the following shall be described:

- Number of cycles administered,
- Cumulative dose (mg/m²),
- Dose intensity (mg/m²/week),
- Relative dose intensity.
- Amendments: Number of dose reductions, interruptions, and the reasons,
- Administration delays and the reasons.

7.4.2 Arm B: Gemcitabine

The following shall be described:

- Number of cycles administered, the number of infusions
- Cumulative dose (mg/m²),
- Dose intensity (mg/m²/week),
- Relative dose intensity.
- Amendments: Number of dose reductions, interruptions, and the reasons,
- Administration delays and the reasons.

7.5 Efficacy

7.5.1 Overall Survival (Primary Endpoint)

Population: ITT

Overall and by treatment arm, the following shall be provided:

- Median follow-up,
- Median overall survival,
- Overall survival rates at 6 and 12 months,
- Number of events observed,
- Number of subjects at risk,

- Associated log-rank test,
- Stratified Cox model on stratification factors (HR and 95% CI) univariate and multivariate,
- Overall survival curves.

7.5.2 Progression-Free Survival

Population: ITT

Overall and by treatment arm, the following shall be provided:

- Median progression-free survival,
- Progression-free survival rates,
- The nature and number of observed events,
- Number of subjects at risk,
- Associated log-rank test,
- Stratified Cox model on stratification factors (HR and 95% CI) univariate and multivariate,
- Progression-free survival curves.

7.5.3 Objective Response Rate and Duration of Response

Population: ITT, Evaluable for Tumor Response

Tumor response was evaluated according to RECIST criteria.

The global response rate from the first evaluation shall be described by treatment arm based on the frequency of each type of response, percentage, and 95% confidence intervals.

The best overall response rate across all evaluations shall be described by the frequency of each type of response and its percentage, with the associated 95% confidence interval for each treatment arm.
Chi-square or Fisher's Exact test (if appropriate) shall be used to compare the treatment arms in terms of response rate.

The median duration of response shall be estimated using the Kaplan-Meier method.

7.6 Tolerability

7.6.1 Treatment Exposure

Treatment exposure shall be assessed by describing the cumulative doses, dose intensity, and relative dose intensity for each drug by patient and treatment arm.

Cumulative Dose (mg/m²):
The cumulative dose (mg/m²) per patient is the total sum of doses administered to the subject during the study, adjusted for the body surface area (Sum of doses (mg) / BSA (m²)).

7.6.1.1 5-FU

Patients in Arm A (FOLFIRINOX) will receive a 400 mg/m² bolus plus a 46-hour continuous infusion of 2.4 g/m² for each cycle (1.2 g/m² on Day 1 and 1.2 g/m² on Day 2) following oxaliplatin, folinic acid, and irinotecan.

The treatment duration for 5-FU (in weeks) during the study is defined as: **[last dosing date – first dosing date + 13] / 7**

Dose intensity and relative dose intensity per patient shall be calculated for 2-week cycles.
Dose intensity (mg/m²/cycle) is defined as:

$$\frac{\text{Cumulative dose of 5-FU (mg/m}^2\text{)}}{\text{Treatment duration for 5-FU (in weeks) / 2}}$$

Relative dose intensity is defined as the dose intensity divided by the expected dose per cycle (2800 mg/m²/2 weeks = cycle).

7.6.1.2 Irinotecan (iri)

Patients in Arm A (FOLFIRINOX) will receive a dose of 180 mg/m² IV as a 90-minute infusion after oxaliplatin.

The treatment duration for irinotecan (in weeks) during the study is defined as: **[last dosing date – first dosing date + 14] / 7**

Dose intensity and relative dose intensity per patient shall be calculated for 2-week cycles.

Dose intensity (mg/m²/cycle) is defined as:

$$\frac{\text{Cumulative dose of IRI (mg/m}^2\text{)}}{\text{Treatment duration for irinotecan (in weeks) / 2}}$$

Relative dose intensity is defined as the dose intensity divided by the expected dose per cycle (180 mg/m²/2 weeks = cycle).

7.6.1.3 Oxaliplatin (oxa)

Patients in the FOLFIRINOX arm (Arm A) will receive a dose of 85 mg/m² IV over 2 hours on Day 1, before any other infusion every 2 weeks.

The treatment duration for oxaliplatin (in weeks) during the study is defined as: **[last dosing date – first dosing date + 14] / 7**

Dose intensity and relative dose intensity per patient shall be calculated for 2-week cycles.

Dose intensity (mg/m²/cycle) is defined as:

$$\frac{\text{Cumulative dose of oxaliplatin (mg/m}^2\text{)}}{}$$

Treatment duration with oxaliplatin (in weeks) / 2

Relative dose intensity is defined as the dose intensity divided by the expected dose per cycle (85 mg/m²/2 weeks = cycle), that is

$$\text{RDI} = \frac{\text{Dose Intensity} = \dfrac{\text{Cumulative dose of oxaliplatin}}{\text{Treatment duration with oxaliplatin (weeks)} / 2}}{\text{Planned dose}} = \frac{\text{Planned dose (mg/m}^2\text{/cycle)}}{\text{Planned dose}}$$

Which can be written as:

$$\frac{\text{Cumulative dose of oxaliplatin}}{\dfrac{[\text{last dosing date} - \text{first dosing date} + 14] / 7}{\text{Planned dose} * \dfrac{\text{Number of cycles}}{14 * \text{number of cycles} / 7}}}$$

7.6.1.4 Gemcitabine (gem)

Patients in the Gemcitabine arm (Arm B) will receive a dose of 1000 mg/m² via a 30-minute strict IV infusion once a week for 7 weeks, followed by 14 days of rest. Then, starting from the next cycle, the administration shall be repeated once a week for 3 consecutive weeks, followed by one week of rest.

The treatment duration for gemcitabine (in weeks) during the study is defined as: **[last dosing date – first dosing date + 7] / 7**

Dose intensity and relative dose intensity per patient shall be calculated weekly.

Dose intensity (mg/m²/week) is defined as:

$$\frac{\text{Cumulative dose of gemcitabine (mg/m}^2\text{)}}{\text{Treatment duration with gemcitabine (in weeks)}}$$

Relative dose intensity is defined as the dose intensity divided by the expected dose per week (1000 mg/m²/week).

7.6.2 Adverse Events (AE)

Evaluable for Tolerability Population

All adverse events related to treatments shall be collected and described according to the predefined groups in the CRF. The severity of AEs shall be graded using the NCI-CTC toxicity scale (version 3.0).

AEs shall be described for each treatment arm by cycle and patient.
Each AE shall be described according to the 5 grades (0, 1, 2, 3, 4) and grades 3/4.

For patient analysis, if an AE is reported more than once during treatment, the most severe grade shall be reported for the patient.
For cycle analysis, if an AE is reported more than once during a treatment cycle, the most severe grade for that cycle shall be reported for the patient.

Chi-square or Fisher's Exact test (if appropriate) shall be used to compare the treatment arms in terms of the incidence of grade 3/4 toxicity.

7.6.3 Biological Data

Biological data were collected during the cycles according to a normal/abnormal scoring.
They shall be described as such for each treatment arm by cycle and patient.
Per patient analysis, if a biological data point is reported as abnormal at least once during treatment, this data shall be reported per patient.
Per cycle analysis, if a biological data point is reported as abnormal at least once during the cycle, this data shall be reported per patient.

7.6.4 WHO Performance Status

Changes in WHO performance status from the inclusion assessment to the end of the study shall be presented by treatment arm.

7.6.5 Weight

Weight, measured at each cycle, shall be analyzed for its changes from the inclusion assessment to the lowest value recorded after the first dose of treatment, and shall be coded according to the CTC-NCI version 3.
The incidence of the worst grade change per patient shall be described by treatment arm. Weight loss and gain shall be described.

Parameter	*Grade 0*	*Grade 1*	*Grade 2*	*Grade 3*	*Grade 4*
Weight gain/weight loss	<5%	5 – <10%	10 – <20%	≥20%	--

7.6.6 Concomitant Treatments

The use of concomitant treatments and their duration during the cycles shall be described and listed by treatment arm.

7.7 Quality of Life

Quality of life shall be assessed using the EORTC QLQ-C30 questionnaire and the validated specific EORTC PAN 24 module.

8 REFERENCES

[1] Haybittle JL: Repeated assessments of results in clinical trials of cancer treatment. Br J Radiol 1971;44:793-7

[2] DuBois D; DuBois EF: A formula to estimate the approximate surface area in height and weight be known. *Arch Int Med* 1916 17:863-71