PRODIGE 35 - FFCD 1403 – PANOPTIMOX

RANDOMISED PHASE II STUDY IN METASTATIC PANCREATIC CANCER EVALUATING FOLFIRINOX +/- LV5FU2 IN MAINTENANCE VERSUS FIRGEM IN FIRST-LINE

Randomised Phase II - multi-centre

EudraCT No. 2014-002574-36

FFCD Intergroup Trial - UNICANCER GI

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LIST OF ABBREVIATIONS

CEA	Carcinoembryonic Antigen
ALT	Alanine aminotransferase (or SGPT: serum glutamic pyruvic transaminase)
ANSM	Agence nationale de sécurité du médicament et des produits de santé (French National Agency for Medicines and Health Products Safety)
CRA	Clinical Research Associate
AST	Aspartate-aminotransferase (or SGOT: serum glutamic-oxaloacetic transaminase)
EC	Ethics Committee
CRF	Case Report Form
CT	Chemotherapy
CTC	Common Toxicity Criteria
EDTA	Ethylene diamine tetracetic acid
EGF	Epidermal Growth Factor
EGFR	Epidermal Growth Factor Receptor
AE	Adverse event
SAE	Serious adverse event
5FU	5-fluorouracil
FFCD	Fédération Francophone de Cancérologie Digestive [Francophone Digestive Cancer Federation]
FOLFIRI	Folinic acid - Fluorouracil - IRInotecan
GDS	Geriatric depression scale
GGT	Gamma glutamyl transpeptidase
Hb	Haemoglobin
HR	Hazard ratio
AHT	Arterial hypertension
INR	International Normalized Ratio
MRI	Magnetic Resonance Imaging
ITT	Intention to treat
IV	Intravenous
D	Day
KM	Kaplan Meier
LDH	Lactate dehydrogenase
ULN	Upper Limit of Normal
MMSE	Mini Mental State Examination
N	Normal
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
CBC	Complete blood count
WHO	World Health Organisation
ALP	Alkaline phosphatase
PNN	Polynuclear neutrophil
Q1-Q3	Quartiles
RECIST	Response Evaluation Criteria In Solid Tumors
CR	Complete Response
PR	Partial Response
OR	Objective Response
PNN	Polymorphonuclear neutrophils
OS	Overall survival
PFS	Progression-free survival
SD	Stable Disease
TAP	Thoracic-Abdominal-Pelvic
CT	Computerized tomography
PT	Prothrombin Time
UICC	Union for International Cancer Control

PROTOCOL ACCEPTANCE FORM

PRODIGE 35 STUDY - FFCD 1403 – PANOPTIMOX
Randomised Phase II Randomised in Metastatic Pancreatic Cancer Evaluating FOLFIRINOX +/- LV5FU2 in Maintenance Versus FIRGEM In First-Line

Randomised Phase II - multi-centre

EudraCT No. 2014-002574-36

Version 2.2 – 18/08/2014

This version of the protocol has been approved by:

The Sponsor: Ms Cécile Girault Date: 18/08/2014 Signature:

The Coordinator: Dr Laetitia Dahan Date: 18/08/2014 Signature:

I, the undersigned, Doctor:

.....

After having read the prerequisites for this research, the protocol and its appendices, agree to conduct this trial in accordance with Good Clinical Practice and in accordance with the applicable provisions of the French Public Health Code.

In particular, I agree to:

- comply with the protocol as well as all changes notified to me by the Sponsor
- supervise the research at the centre and provide training to my colleagues on how to conduct the research and provide a list of named colleagues
- ensure that each patient signs a written consent form after reading the patient information leaflet, before carrying out any research procedures
- report serious adverse events or new information within 24 hours of becoming aware of their occurrence, in compliance with the indications set out in the research protocol
- comply with the inclusion and exclusion criteria, as well as the study start and end dates
- participate in the biological part of the study, subject to the patient signing the specific consent form, and to send the samples in accordance with recommendations
- complete all items on the case report form, oversee the quality of the data collection, and manage products correctly
- retain research-related data and documents for a period of 15 years after the end of the study

- notify the Sponsor of any conflicts of interest likely to jeopardise my scientific independence under the scope of the research
- notify the Sponsor immediately of any amicable or contentious proceedings brought by any person involved in the research or his/her beneficiaries, likely to implicate the liability of the sponsor
- accept regular visits from the sponsor's representatives, and make available to them all source documents and materials related to the research, to check the quality of data recorded on the case report form. I agree to a review in the form of an audit carried out by the Sponsor and/or an inspection by the heath authorities
- answer by phone or mail any requests for corrections or clarifications relating to the case report form
- provide sufficient time to allow the FFCD CRA to sign the forms, answer any questions and take the required actions.

Date: Signature:

STAMP OF THE CENTRE:

Send the original document to CRGA at the FFCD – 7 bd Jeanne d'Arc – BP 87900 – 21079 Dijon Cedex, France

SYNOPSIS

Title	**PRODIGE 35 - PANOPTIMOX** **Randomised Phase II Randomised in Metastatic Pancreatic Cancer Evaluating FOLFIRINOX +/- LV5FU2 in Maintenance Versus FIRGEM In First-Line**
Sponsor	Fédération Francophone de Cancérologie Digestive (FFCD)
Study design	**Arm A: FOLFIRINOX** FOLFIRINOX every 2 weeks until progression or occurrence of unacceptable toxicity (a maximum of 12 courses is recommended). **Arm B: FOLFIRINOX with maintenance via LV5FU2** 4 months (8 courses) of FOLFIRINOX then, if the disease has not progressed, LV5FU2 as maintenance until progression (resumption of FOLFIRINOX if progression) **Arm C: FIRGEM** Alternating 2 months of FOLFIRI3 (4 cures) with 2 months of gemcitabine (1000 mg/m²/week). 3/4 weeks (2 courses) until progression or unacceptable toxicity
Study endpoints	**Primary endpoint:** The primary endpoint of this Phase II study is to evaluate the rate of patients alive and without radiological (RECIST V1.1) and/or clinical progression after 6 months in each arm, and to select the best therapeutic strategy for a future Phase III study. **Secondary outcomes:** - Duration of disease control - Progression-free survival - Time to progression during the maintenance treatment - Median time of maintenance treatment (arm B) - Objective response rate - Overall survival - Toxicity (NCI-CTC V4.0) - Overall survival - Rate of patients receiving a 2nd line therapy - Quality of life (EORTC QLQ-C30 questionnaire) - Geriatric fragility factors predictive of treatment failure in patients over the age of 65 years
Methodology	Multi-centre, open-label, randomised Phase II study
Inclusion criteria	• Pancreatic adenocarcinoma, confirmed by histology or cytology. • Metastatic disease • At least one measurable lesion according to RECIST V1.1 criteria

	• No prior chemotherapy (adjuvant chemotherapy with gemcitabine or LV5FU2 permitted if administered more than 6 months prior to inclusion) • No prior chemotherapy (except if there is at least one measurable lesion outside of the irradiation area) • Age ≥ 18 years and ≤ 75 years • General condition: WHO 0-1 • PNN ≥ 1500/mm^3, platelets ≥ 100 000/mm^3 • Bilirubin ≤ 1.5 times ULN, creatinine < 120 µmol/L • Patient information leaflet and signed consent form
Non-inclusion criteria	• Another type of pancreatic tumours, especially endocrine tumour or involving acinar cells • Ampulloma • Cerebral or meningeal metastasis • Gilbert's Disease • Neuropathy ≥ grade 1 • Specific contraindications to the study treatments • History of chronic diarrhoea or inflammatory disease of colon or rectum, or bowel obstruction or bowel sub-obstruction not resolved with symptomatic treatment • Active progressive infection or another serious underlying condition likely to prevent the patient from receiving the treatment • Another concomitant cancer or a history of cancer within the last 5 years, except for *in situ* cancer of the neck of the uterus, or basal cell carcinoma, squamous cell carcinoma, considered as resolved • Significant previous cardiac and respiratory disease • Patient already enrolled in another therapeutic study with experimental treatment • Men and women of child-bearing potential not using an effective method of contraception • Pregnant women or women likely to become pregnant, or breast-feeding

	• Patient under guardianship, safeguarding or legal protection measures, and persons deprived of liberty • Impossibility due to geographical, social or psychological reasons of complying with the follow-up schedule of the trial.
Biological study	A biological study will evaluate: - Constitutional genetic polymorphisms with an influence on the efficacy and tolerance of chemotherapy molecules (UGT1A1, ERCC1, GSTT1, MTHFR, DPD, TS, etc.). - A paraffin section study to identify immunohistochemical biomarkers predictive of response to treatment
Statistical methodology	The statistical analysis will involve all randomised intention-to-treat patients. Qualitative variables will be described in the form of numbers and percentage of the population concerned, with a 95% confidence interval. Quantitative variables are described using averages, standard deviations, medians and interquartile ranges, based on the type of distribution. For Phase II, the rate of patients alive and progression-free at 6 months will be described and a 95% confidence interval calculated using an exact test method. (Newcombe, SIM 1998). The Kaplan Meier method will be used to estimate overall survival in each arm. A description will be given of survival percentages at different times, with a 95% confidence interval. Median follow-up will be calculated using an inverse Kaplan Meier method (Shemper, 1996). Tolerance will be described using NCI-CTC 4.0.
Calculation of sample size	Clinical assumptions for the calculation of the sample size are as follows: - H_0: rate of patients alive and progression-free at 6 months = 30%, no benefit - H_1: rate of patients alive and progression-free at 6 months >30%, benefit A 45% rate is expected. Based on a Fleming's one-step plan (α=5%, power = 90%), 87 are to be randomised in each arm. Taking into account a 5% rate of patients lost to follow-up and non-evaluable, 92 patients/arm will be randomised. **Total = 276 patients** Decision-making rules will only be applied to arms B and C. Arm A (FOLFIRINOX) is the reference arm. Out of the 87 evaluable patients: - If 33 patients or fewer are alive and progression-free at 6 months, the treatment will be considered as not effective - If 34 patients or more are alive and progression-free at 6 months, the treatment will be considered as effective .
Length of inclusion and participation of each patient	Number of patients required: 276 Number of centres: 60 Start of inclusions: December 2014 End of inclusions: December 2016 Analysis: June 2017

SCHEDULE OF EXAMINATIONS AND FOLLOW-UP

	BEFORE TREATMENT	DURING TREATMENT and in the event of discontinuation of treatment without progression (e.g. toxicity or patient refusal)						AFTER DISCONTINUATION OF TREATMENT due to progression (failure of strategies)
		Arms A and B		Arm C				
	In the 8 days prior to inclusion (except for CT)	Before each course	On D8 of each course	FOLFIRI3 Before each course	FOLFIRI3 On D8 of each course	GEMCITABINE Before each administration	Every 8 weeks and 30 days after the last administration of CT, regardless of the arm	Every 6 months until death
Clinical and biological informed consent	X							
CLINICAL EXAMINATION								
Weight, body surface area	X	X		X		X	X	X
Height	X							
WHO general condition	X	X		X		X	X	X
Toxicity Assessment NCI-CTCAE version 4.0		X	X	X	X	X	X	X
QLQ-C30	X						X	X
Geriatric assessment for in patients over 65 years[1]	X						X	
LAB TEST ASSESSMENT								
Lab test assessment	X[2]	X[4]	X[4]	X[5]	X[5]	X[5]	X[2]	
Pregnancy test	X							
CA19 -9 and CEA markers	X						X	
PARA-CLINICAL EXAMINATIONS								
Thoracic-Abdominal-Pelvic CT scan	**X**[3]						**X**	X
ECG	X[3]							
ANCILLARY BIOLOGY STUDY								
2 EDTA tubes of 5 or 7 mL of blood	X							
Biopsies, or tumour block, fixed in paraffin	X							

[1]: Oncodage score (G8), Charlson Index, MMSE, GDS (short version)

[2]: Full lab test assessment: CBC, platelets, PT, serum sodium, serum potassium, calcium, bilirubinaemia (total and conjugated), blood creatinine, blood glucose, AST, ALT, alkaline phosphatase, LDH, protein in serum, blood albumin

[3]: In the 3 weeks prior to inclusion.

[4]: ARMS A and B:
Before each chemotherapy course: CBC, platelets, bilirubinaemia (total, unconjugated and conjugated), Every month (uneven courses), add blood albumin, serum sodium, potassium serum, blood creatinine, blood glucose
On D8 of each course of FOLFIRINOX: CBC, platelets. If required, administer growth factors for subsequent courses.
On D8 of the 1st course: blood creatinine, potassium serum and serum sodium. In Arm B, no systematic blood count on D8 of LV5FU2.

[5]: ARM C:
Before each FOLFIRI3 course: CBC, platelets, bilirubinaemia (total, unconjugated and conjugated), Every month (uneven courses), add blood albumin, serum sodium, potassium serum, blood creatinine, blood glucose
On D8 of each course of FOLFIRI3: CBC, platelets
Before each course of gemcitabine: CBC, platelets, bilirubinaemia (total, unconjugated and conjugated), AST, ALT

Study endpoints

Primary endpoint

The primary endpoint is to evaluate the rate of patients alive and without radiological (RECIST V1.1) and/or clinical progression after 6 months in each arm, and to select the best therapeutic strategy for a future Phase III study.

Secondary endpoints

The secondary endpoints of the study are:

- Duration of disease control (see definition below)
- Progression-free survival
- Time to progression during maintenance
- Median time of maintenance treatment (arm B)
- Objective response rate according to RECIST 1.1 criteria at 2, 4 and 6 months
- Best response to treatment
- Overall survival
- Tolerance of treatment (toxicity according to NCI-CTC V4.0), with particular attention to neurotoxicity grades and frequency of use of haematopoietic growth factors for haematological toxicity
- Percentage of patients receiving a 2nd line therapy
- Quality of life (QLQ-C30 EORTC v3.0 questionnaire)
- Geriatric fragility factors predictive of treatment failure in elderly subjects ≥ 65 years

In arm A (Folfirinox), duration of disease control is defined as the period of time between the randomisation date and the date of progression under treatment (clinical and/or radiological) or death (for any reason and at any time) or the date of switching lines.

In arm B with maintenance (arm B), duration of disease control is defined as follows:

- After progression during maintenance with LV5FU2 (PFS1), if the disease is not controlled after reintroduction of FOLFIRINOX (PFS2) then the duration of disease control is equal to the period of time between randomisation and progression before the reintroduction of FOLFIRINOX (PFS1).

- After progression during maintenance with LV5FU2 (PFS1), if the disease is not controlled after reintroduction of FOLFIRINOX then the duration of disease control is equal to the period of time between randomisation and progression (PFS2) with FOLFIRINOX (PFS1 + PFS2).

In the FIRGEM arm (arm C), duration of disease control is defined as follows:
If discontinuation of alternate treatments (FOLFIRI.3/Gemcitabine) is due to progression (PFS1) then:

- If the disease is not controlled after changing the treatment then the duration of disease control is equal to the period of time between randomisation and progression before changing the treatment (PFS1).
- If the disease is again controlled after changing the treatment, then the duration of disease control (stability, OR) is equal to the period of time between randomisation and progression (PFS2) with the treatment (PFS1 + PFS2)

If the alternation of treatments is discontinued for a reason other than progression (e.g. toxicity, decision of the investigator, etc.), then the duration of disease control will be the period of time up to the first progression (PFS1).

Ancillary biology studies:

- Blood sample study of constitutional genetic polymorphisms with an influence on the efficacy and tolerance of chemotherapy molecules (UGT1A1, ERCC1, GSTT1, MTHFR, DPD, TS, etc.).
- A paraffin section study to identify immunohistochemical biomarkers predictive of response to treatment.

Patient selection at enrolment

Inclusion criteria

- Pancreatic adenocarcinoma, confirmed by histology or cytology.
- Metastatic disease
- At least one measurable lesion according to RECIST V1.1 criteria
- No neuropathy
- No prior chemotherapy (adjuvant chemotherapy with gemcitabine or LV5FU2 permitted if administered more than 6 months prior to inclusion)
- No prior chemotherapy (except if there is at least one measurable lesion outside of the irradiation area)
- Age $\geq$ 18 years and $\leq$ 75 years

- General condition: WHO 0-1
- Satisfactory haematological function: PNN ≥ 1500/mm^3, platelets ≥ 100 000/mm^3
- Satisfactory liver function: bilirubin ≤ 1.5 times ULN
- Satisfactory kidney function: creatinine < 120 µmol/L
- Absence of heart failure or non-medically controlled angina pectoris or myocardial infarction within 6 months prior to inclusion
- Patient information leaflet and signed consent form

Non-inclusion criteria

- Another type of pancreatic tumours, especially endocrine tumour or involving acinar cells
- Ampulloma
- Gilbert's Disease
- Neuropathy ≥ grade 1 (NCI-CTC version 4.0)
- Cerebral or meningeal metastasis
- Specific contraindications to the study treatments
- History of chronic diarrhoea or inflammatory disease of colon or rectum, or bowel obstruction or bowel sub-obstruction not resolved with symptomatic treatment
- Active progressive infection or another serious underlying condition likely to prevent the patient from receiving the treatment
- Another concomitant cancer or a history of cancer within the last 5 years, except for *in situ* cancer of the neck of the uterus, or basal cell carcinoma, squamous cell carcinoma, considered as resolved
- Significant previous cardiac and respiratory disease
- Patient already enrolled in another therapeutic study with experimental treatment
- Pregnant women or women likely to become pregnant, or breast-feeding
- Patient under guardianship, safeguarding or legal protection measures, and persons deprived of liberty Impossibility due to geographical, social or psychological reasons of complying with the follow-up schedule of the trial.

BASELINE ASSESSMENT

A baseline assessment is required in the 8 days prior to initiation of treatment, except for para-clinical assessments which may be performed within 3 weeks prior to randomisation.

Full clinical examination including:

- Measurement of weight, height, body surface area and vital signs (temperature, pulse, blood pressure)
- WHO index

Lab tests performed less than 7 days previously:

- CBC, platelets, PT, sodium, potassium, calcium
- Total bilirubin (unconjugated and conjugated), ALT, AST, alkaline phosphatase, LDH
- Blood creatinine, blood glucose
- Protein in serum, blood albumin
- Marker: CA 19-9, CEA
- Pregnancy test if women of childbearing potential

Quality of Life questionnaire:

- QLQ-C30 to be completed by the patient before randomisation (on the same day or within 15 days prior to randomisation but before the first course)

Geriatric assessment for patients aged over 65 years:

- ONCODAGE score (G8)
- Charlson Index
- Mini-Mental State Examination (MMSE)
- Short version of the Geriatric Depression Scale (GDS 15 to be completed by the patient)

Morphological and para-clinical examination in the **3 weeks** prior to inclusion:

- Thoracic-Abdominal-Pelvic (CT PET) scan carried out less than 3 weeks earlier
- ECG

Biological study:

- Collection of 2 EDTA tubes of 5 (or 7) ml of blood (for genotyping UGT1A1, ERCC1, GSTT1, MTHFR, DPD, TS and CDA1)

RANDOMISATION

After signing the consent form and validating the results of the initial baseline assessment, eligible patients will be randomised at the **Centre de Randomisation – Gestion – Analyse (CRGA) of the FFCD**.

The investigator is required to fax the completed and signed randomisation form to the CRGA at the FFCD:

from Monday to Friday from 9 a.m. to 6 p.m.
Fax: + 33 (0)3 80 38 18 41 / Tel: + 33 (0)3 80 66 80 13

Confirmation of randomisation will be faxed back to the investigator with the patient registration number and arm allocated by randomisation.

After randomisation of study patients, treatment should begin within 10 days.

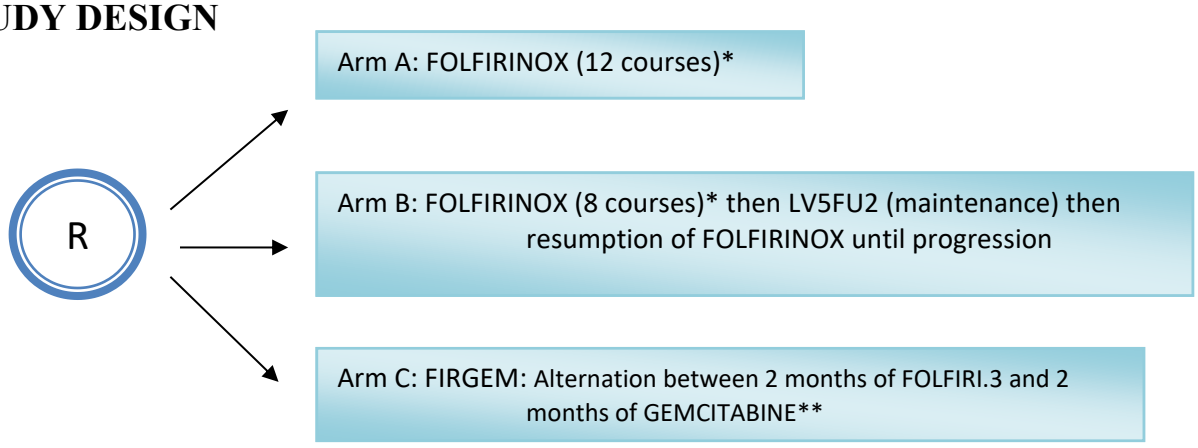
A case report form will be forwarded at the opening of the centre. A new case report form will then be sent after each randomised patient.

Stratification

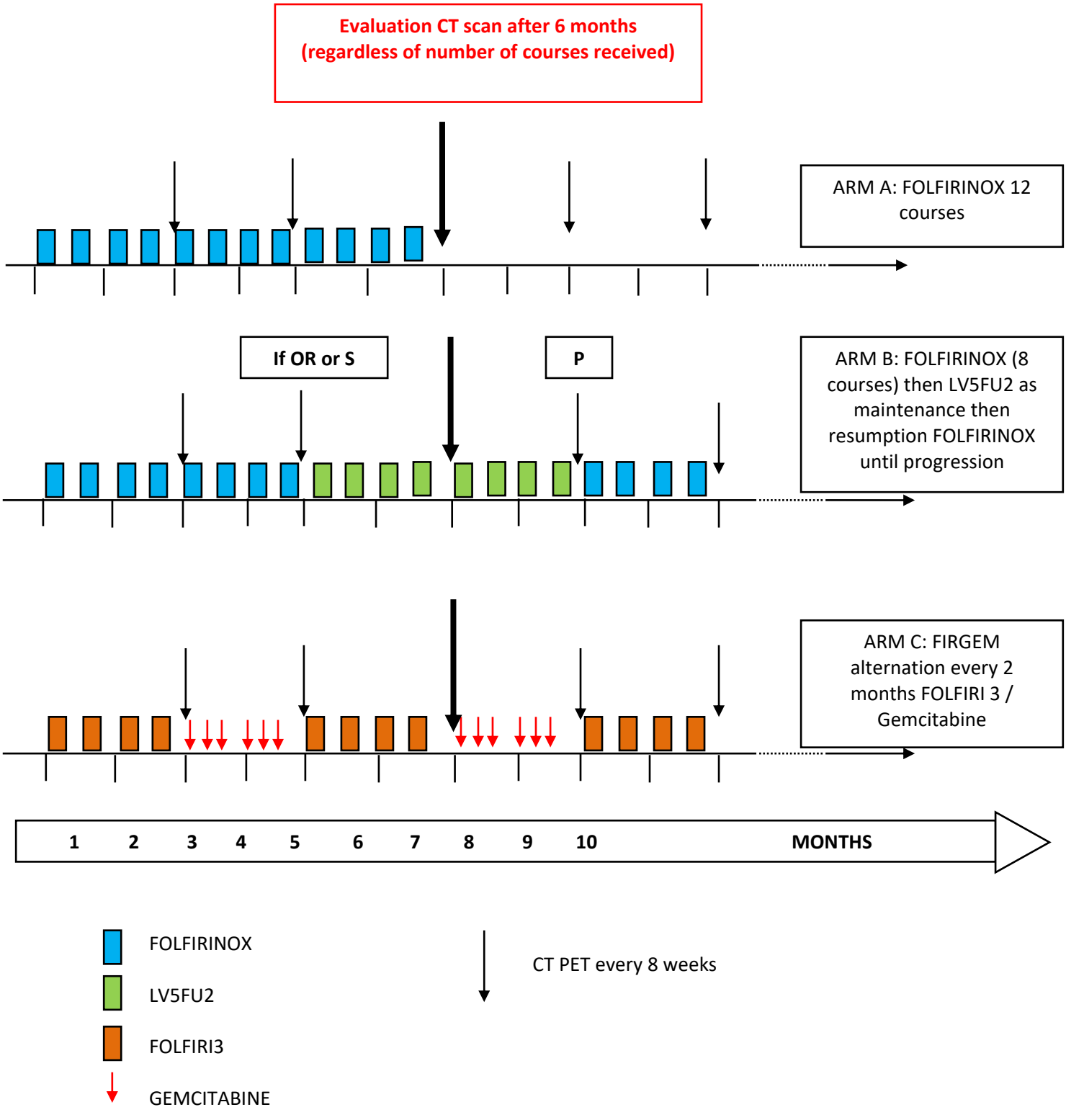
Patients will be randomized (1:1:1) according to the minimisation technique based on the following **stratification factors**:

- Centre
- Biliary stent: Yes versus No
- Age: ≤ 65 years versus > 65 years

STUDY DESIGN



*unless progression or unacceptable toxicity
**** in case of progression, limiting toxicity with one of the 2 treatments, continuation of the other treatment until progression or unacceptable toxicity


Evaluation CT scan after 6 months
(regardless of number of courses received)
ARM A: FOLFIRINOX 12 courses
If OR or S
P
ARM B: FOLFIRINOX (8 courses) then LV5FU2 as maintenance then resumption FOLFIRINOX until progression
ARM C: FIRGEM alternation every 2 months FOLFIRI 3 / Gemcitabine
1 2 3 4 5 6 7 8 9 10 MONTHS
FOLFIRINOX
LV5FU2
FOLFIRI3
GEMCITABINE
CT PET every 8 weeks

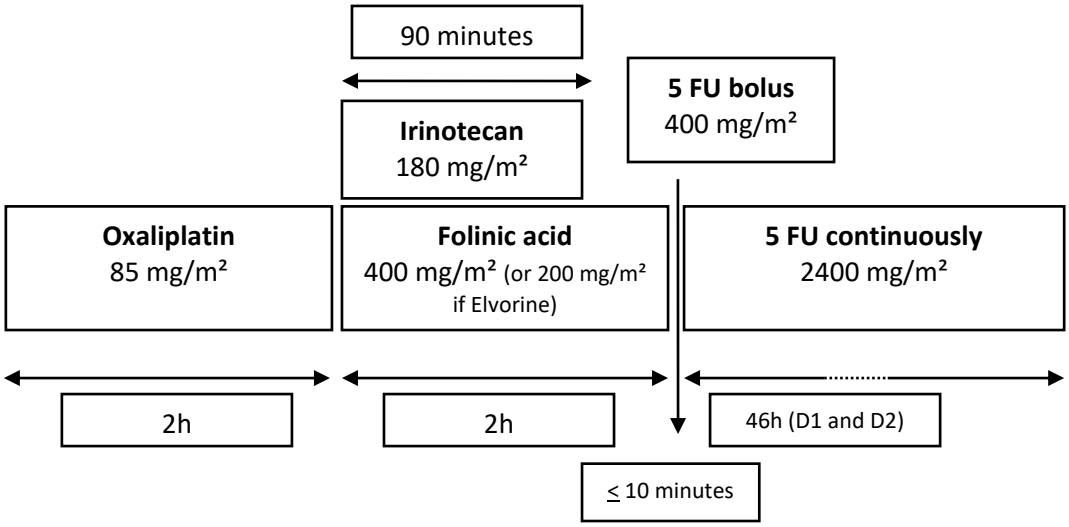
TREATMENTS

Treatments are not supplied under the scope of the study.

FOLFIRINOX (Arm A)

FOLFIRINOX, courses administered every 2 weeks and a maximum of 12 courses. Subsequent treatments will left to the discretion of the investigator.

- Oxaliplatin 85 mg/m^2 D1 over 2 hours then
- Irinotecan 180 mg/m^2 D1 over 90 minutes
- Folinic acid 400 mg/m^2, D1 over 2 hours (during the irinotecan perfusion)
- 5-FU bolus 400 mg/m² D1 followed by 5-FU continuously 2400 mg/m^2 in **total** over 46 hours, **i.e. 1200 mg/m^2 on D1 and 1200 mg/m² on D2.**



Treatment starts with the IV administration (2-hour infusion) of oxaliplatin at a dose of 85 mg/m², followed by the simultaneous IV administration (2-hour infusion) of folinic acid at a dose of 400 mg/m² and irinotecan at a dose of 180 mg/m² (IV infusion for 1 hour 30 min), to start immediately after the end of the oxaliplatin infusion. 5-FU is administered immediately after the infusion of folinic acid at a dose of 400 mg/m^2 as a 5-minute IV bolus, followed by continuous 5FU infusion over 46 hours at 2400 mg/m^2.
Warning: if the patient presents with cholinergic syndrome, secondary to irinotecan, atropine sulphate should be administered unless its use is contraindicated (see SmPC, Appendix 7). Atropine sulphate should then be used as prophylaxis for the next courses.

Treatment will continue for a maximum of 12 courses, until:

- disease progression

- onset of unacceptable toxicity or
- patient refusal.

Further treatment is left to discretion of the investigator.

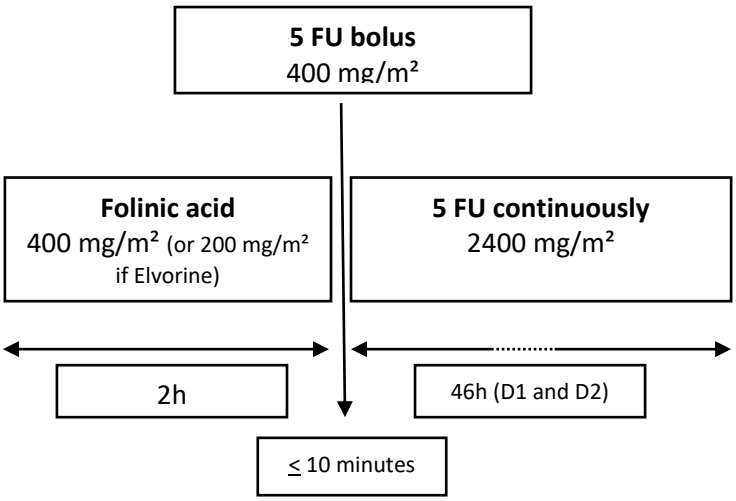
FOLFIRINOX with maintenance via simplified LV5FU2 (Arm B)

FOLFIRINOX for 4 months (8 courses, 1 course every 2 weeks), then if the disease is controlled (stability or objective response (CR or PR)), simplified LV5FU2 (1 course every 2 weeks) as maintenance until progression.

FOLFIRINOX at the same doses as described above for arm A.

Simplified LV5FU2 as maintenance until progression:

- Folinic acid 400 mg/m² (200 mg/m² if Elvorine), as a 2-hour infusion followed by
- 5FU 400 mg/m² as a 10-minute bolus, followed by 5FU 2400 mg/m² as a 46-hour infusion.



If progression during the maintenance treatment, patients should start taking (unless contraindicated or refusal) a FOLFIRINOX regimen, until:

- disease progression
- onset of unacceptable toxicity or
- patient refusal

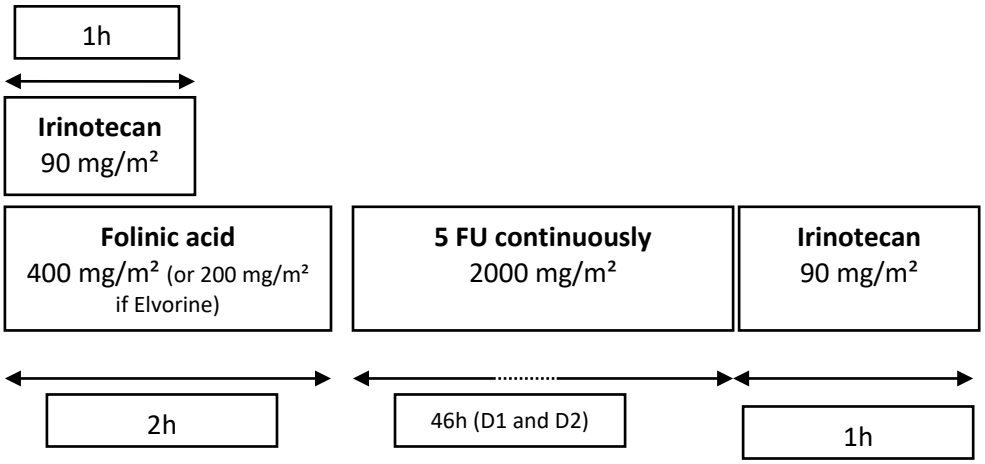
Further treatment is left to discretion of the investigator.
Warning: if the patient presents with cholinergic syndrome, secondary to irinotecan, atropine sulphate should be administered unless its use is contraindicated (see SmPC, Appendix 7). Atropine sulphate should then be used as prophylaxis for the next courses.

FIRGEM (Arm C)

Alternation every 2 months of FOLFIRI.3 (4 courses, 1 course every 2 weeks) and gemcitabine 1000 mg / m^2 (2 cycles of 3 courses, one course per week, 3 weeks out of 4).

FOLFIRI.3:

- Irinotecan 90 mg/m² on D1 as a 60-minute infusion with folinic acid
- Folinic acid 400 mg/m² (or 200 mg/m² Elvorine) on D1 as a 2-hour infusion
- 5FU continuously 2000 mg/m² for 46 hour
- Then irinotecan again at a dose of 90 mg/m² (1h) on D3, at the end of the 5-FU infusion



Warning: if the patient presents with cholinergic syndrome, secondary to irinotecan, atropine sulphate should be administered unless its use is contraindicated (see SmPC, Appendix 7). Atropine sulphate should then be used as prophylaxis for the next courses.

GEMCITABINE:

- 1000 mg/m^2 as a 30-minute infusion on D1, D8, D15, D29, D36 and D43 for 2 months (1 injection per week for 3 weeks followed by 7 days of rest (1 week) and then resumption of 1 injection per week for 3 weeks).

In case of progression, limiting toxicity with one of the two treatments, it is recommended (unless contraindicated or refused) to continue the other treatment until progression, unacceptable toxicity or patient refusal.

Further treatment is left to discretion of the investigator.

DOSE ADJUSTMENT ACCORDING TO TOXICITY

General principles:
- All chemotherapy drugs should be administered on the day of the course, as long as the following criteria are respected:

  - PNN $\geq$ 1500/mm^3
  - Platelets $\geq$ 100,000/mm^3
  - Gastrointestinal toxicity $\leq$ grade 1

- If these criteria are not met, the course must be postponed for one week.
- Treatment will resume with a dose adjustment according to the tables below and according to the maximum grade of toxicity observed in the period between courses.

Treatment with 5FU should be discontinued in case of angina pectoris or myocardial infarction related to the 5FU treatment.
- Treatment with 5FU should be reduced by 50% in case of serious liver function disorders.
- Treatment with 5FU should be reduced by 50% in case of granulocytopenia between 2,000 and 3,000/mm3 or thrombocytopenia below 100,000/mm3. Treatment discontinuation should be considered if granulocytopenia is less than 2000/mm3 or thrombocytopenia less than 80,000/mm3.
- Irinotecan treatment should be discontinued if bilirubinaemia is above 3x ULN (upper limit of normal). It should be reduced by 40% if the bilirubinaemia elevation is between 1.5 and 3x ULN.

Arm A and B FOLFIRINOX +/- LV5FU2:

Toxicity observed on the day of the course

Haematological toxicity on the day of the course	**POSTPONED COURSE**	**DOSE REDUCTION**		
		Irinotecan	**Oxaliplatin**	**LV5FU2**
PNN $\geq$ 1,500/ mm^3 and platelets $\geq$ 100,000/mm^3	No postponement of course	No dose reduction		
PNN < 1500/mm^3	Postpone treatment until PNN $\geq$ 1,500/mm^3 (until D22 or D29 if necessary) and resume the course with G-CSF. If not recovered on D29, discuss discontinuation of treatment, growth Factor, or maintenance alone of LV5FU2	1st episode: reduce dose to 150 mg/m^2 2nd episode: maintain dose at 150 mg/m^2 3rd episode: **Discontinue treatment or maintenance LV5FU2**	1st episode: no dose reduction 2nd episode: reduce dose to 60 mg/m^2 3rd episode: **Discontinue treatment or maintenance LV5FU2**	1st episode: No dose reduction
Platelets < 100,000/mm^3	Until recovery (platelets $\geq$ 100,000/mm^3). If not recovered on D29,	1st episode: no dose reduction	1st episode: reduce dose to 60 mg/m²	1st episode: no

	discuss **discontinuation of treatment**	2nd episode: reduce dose to 150 mg/m^2 3rd episode: **discontinue treatment**	2nd episode: maintain reduced dose 3rd episode: **discontinue treatment**	reduction of dose 2nd episode: reduce the continuous infusion dose by 25%

Maximum toxicity observed during courses

EVENTS	REDUCE DOSE AT NEXT COURSE
- Isolated febrile neutropenia* -Grade 4 neutropenia > 7 days - Infection with concomitant grade 3-4 neutropenia	**1st episode**: reduce the dose of irinotecan to 150 mg/m² and add G-CSF **2nd episode**: also reduce the dose of oxaliplatin to 60 mg/m² **3rd episode**: discuss growth factors or reducing the treatment up to a level of maintenance alone with LV5FU2
Grade 3-4 thrombocytopenia	**1st episode**: reduce the dose of oxaliplatin to 60 mg/m² **2nd episode**: also reduce the dose of irinotecan to 150 mg/m² and the dose of continuous 5-FU by 25% **3rd episode**: **discontinue oxaliplatin and irinotecan, continue LV5FU2**

***Definition**: fever during a period of bone marrow hypoplasia (PNN <500/mm^3) with temperature > 38.5°C. Treatment will continue at the same doses, but with the addition for all remaining courses of G-CSF from D5 to D10. The first dose should not be administered within 24 hours following the end of the cytotoxic chemotherapy.

Gastrointestinal toxicity

EVENTS	REDUCE DOSE AT NEXT COURSE
-Isolated grade **3-4** diarrhoea or -Diarrhoea + fever and/or grade 3-4 neutropenia	**1st episode**: reduce the dose of irinotecan to 150 mg/m² **2nd episode**: also reduce the dose of oxaliplatin to 60 mg/m² and the dose of continuous 5-FU by 25% **3rd episode**: **discontinue irinotecan**
Resistant diarrhoea (> 48 h) despite anti-diarrhoea treatment	No reduction in the dose of irinotecan or oxaliplatin nor 5-FU after recovery unless grade 3-4 diarrhoea or diarrhoea + fever and/or grade 3-4 neutropenia

In the event of haemorrhagic gastrointestinal ulceration or not, the 5 fluorouracil treatment should be discontinued until symptoms have disappeared.

Other toxicity

Mucositis, “head-foot” syndrome: grade 3-4, reduce the continuous 5-FU by 25% for the next courses

Toxicity specific to oxaliplatin: peripheral neuropathy

Toxicity	**Toxicity duration**		
	≤ 7 days	**> 7 days et < 14 days**	**Persistent between courses**
Paraesthesia/dysesthesia with no functional alteration (grade 1 NCI)	No change	No change	No change
Paraesthesia/dysesthesia with functional alteration but no affecting activities of daily living (grade 2 NCI)	No change	No change	**65 mg/m²**
Paraesthesia/dysesthesia with pain or functional alteration affecting activities of daily living (grade 3 NCI)	**65 mg/m²**	**65 mg/m²**	Discontinue
Persistent paraesthesia/dysesthesia, invalidating	N/A	N/A	Discontinue
Acute dysesthesia laryngopharyngeal	Extend the next infusion time to 6 hours. Add (if not already done) 1 g of calcium gluconate and 1 g of magnesium sulphate 15 minutes before the oxaliplatin infusion, infusions to be repeated until the end of the oxaliplatin infusion		

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

Arm C FIRGEM (FOLFIRI 3 and GEMCITABINE)

Adjustment table for FOLFIRI 3 - Toxicity between courses

Toxicity/NCI Grade	**1**	**2**	**3-4**
Anaemia	No dose reduction	No dose reduction	No dose reduction
Neutropenia Thrombocytopenia	No dose reduction	No dose reduction*,**	- 5-FU 1600 mg/m² (48h) - Irinotecan 80 mg/m² on D1 and D3 - Gemcitabine 800 mg/m²
Diarrhoea	No dose reduction	No dose reduction*,**	- 5-FU No dose reduction - Irinotecan 80 mg/m² on D1 and D3
Other ***	-	-	- 5-FU 1600 mg/m² (48h) - Irinotecan 80 mg/m² on D1 and D3 - Gemcitabine 800 mg/m²

* after recovery (grade 0 or 1 toxicity)
** if no recovery after 2 weeks: (persistent diarrhoea or neutropenia > Grade 2 or thrombocytopenia > Grade 1), same dose reduction as for Grade 3-4.
*** except alopecia, cholinergic syndrome, nausea / vomiting without adequate treatment

The introduction of growth factors (EPO and G-CSF) is recommended in case of haematological toxicity, as per the marketing authorisation for these products.

Adjustment table for GEMCITABINE - Toxicity between courses

Haematological toxicity (weekly evaluation)	**DELAYED COURSE**	**DOSE REDUCTION**
PNN > 1,000/mm^3 and platelets > 100,000/mm^3	No delayed course	Administer 100% of the total dose
500 < PNN ≤ 1,000/ mm^3 or 50,000< platelets ≤ 100,000 mm^3	No delayed course	Administer 75% of the total dose (25% dose reduction)
PNN ≤ 500/ mm^3 or platelets ≤ 50,000/ mm^3	Delay the course until PNN ≥ 500/mm^3 and platelets ≥ 50,000/mm^3	No dose reduction

PNN: Polynuclear neutrophils

Hepatic toxicity for Gemcitabine

Increased hepatic transaminases are frequently observed.

- If transaminases (ALT or AST or both) increase by at least 5 x ULN gemcitabine is continued with any reduction in dose.
- If transaminases (ALT or AST or both) increase between 5 and 20 x ULN reduce the gemcitabine dose by 25%
- If transaminases (ALT or AST or both) increase by more than 20 x ULN gemcitabine should be discontinued permanently.

ULN: upper limit of normal

Adjustment of Irinotecan doses for elevation of bilirubinaemia

Irinotecan treatment should be discontinued if bilirubinaemia is above 3x ULN (upper limit of normal). It should be reduced by 40% if the bilirubinaemia elevation is between 1.5 and 3 x ULN. In all cases, obstruction of bile ducts should be investigated and treated, if possible.

Pre-medication, concomitant treatments and contraindicated treatments

Treatments considered necessary for the patient's well-being may be administered at the investigator's discretion.

If the patient presents with cholinergic syndrome, secondary to irinotecan, atropine sulphate should be administered unless its use is contraindicated (see SmPC, Appendix 7). Atropine sulphate should then be administered as prophylaxis for the next courses.

The subcutaneous administration of a growth factor is permitted.
According to EORTC 2010 recommendations [38], the risk of febrile neutropenia should be assessed before each chemotherapy course. Validated risk factors are age > 65 years, history of febrile neutropenia and advanced disease (which is the case for all patients included in this trial).

In case of severe neutropenia, i.e. grade 3-4, patients are at high risk of febrile neutropenia and infection especially in the presence of concomitant diarrhoea. If these symptoms appear, the dose can be adjusted during the next course, and the prescription of haematopoietic growth factors considered.
Administration of haematopoietic growth factors is not routinely recommended for the 1st course of FOLFIRINOX or FOLFIRI3 but may be indicated on a case-by-case basis depending on the clinical condition of the patient. Treatment with lenograstim (GRANOCYTE®), filgrastim (Neupogen®, ZARZIO®) or pegfilgrastim (NEULASTA®) is then recommended.

Contraindicated treatments:
With 5 FU: yellow fever vaccine, live attenuated vaccines, phenytoin for prophylactic use.
With irinotecan: combination with St John's Wort, yellow-fever vaccine.

MONITORING OF PATIENTS

Before each course:

Arms A and B: FOLFIRINOX and FOLFIRINOX with LV5FU2 as maintenance
Patients treated with FOLFIRINOX will be reviewed for a clinical assessment before each course to assess any toxicity and determine the resumption of treatment.

Before each course, every 14 days:

- Clinical examination: weight, WHO and vital signs (temperature, pulse, blood pressure. This examination should be adapted to each patient, at the discretion of the investigator.
- Evaluation of tolerance (toxicity according to NCI-CT V4.0)
- Laboratory test assessment:
  - Before each course: CBC, platelets; total, unconjugated and conjugated bilirubinaemia
  - On D8 of each course of FOLFIRINOX: CBC, platelets. If required, anticipate the administration of growth factors for subsequent courses. On D8 of the 1st course and subsequently, if the investigator deems useful: blood creatinine, potassium serum and serum sodium. A blood count is not systematically required on D8 of LV5FU2 in arm B.
  - Every month (uneven courses): in addition to CBC, platelets and bilirubinaemia , measure blood albumin, serum sodium, potassium serum, blood creatinine, blood glucose

However, depending on tolerance, additional consultations may be required.

Arm C: FIRGEM
Patients treated with gemcitabine will be reviewed for a clinical assessment before each administration to assess any toxicity and determine the continuation of treatment

Before each administration of FOLFIRI.3, every 15 days:

- Clinical examination: weight, WHO and vital signs (temperature, pulse, blood pressure. This examination should be adapted to each patient, at the discretion of the investigator.
- Evaluation of tolerance (toxicity according to NCI-CT V4.0)
- Laboratory test assessment:
  - Before each course: CBC, platelets, total, unconjugated and conjugated bilirubinaemia, blood creatinine, serum sodium, potassium serum, total protein.
  - On D8 of each course: CBC, platelets
  - Every month (uneven courses): in addition to CBC, platelets and bilirubinaemia , measure blood albumin, serum sodium, potassium serum, blood creatinine, blood glucose

Before each administration of gemcitabine: every 7 days:

- Clinical examination: weight, WHO and vital signs (temperature, pulse, blood pressure. This examination should be adapted to each patient, at the discretion of the investigator.
- Evaluation of tolerance (toxicity according to NCI-CT V4.0)
  Laboratory test assessment: CBC, platelets, total, unconjugated and conjugated bilirubinaemia, AST, ALT.

Evaluation every 8 weeks (for the three treatment arms) and/or within 30 following the final CT course

Patients will be evaluated every 8 weeks, i.e.:

- Clinical examination: weight, WHO and vital signs (temperature, pulse, blood pressure. This examination should be adapted to each patient, at the discretion of the investigator.
- Lab testing: CBC, platelets, bilirubin (total, unconjugated and conjugated), PT, ALP, AST, ALT, sodium, potassium, calcium, blood glucose, creatinine, protein in serum, blood albumin, LDH
- Markers: CA 19-9, CEA
- Evaluation of toxicity from the previous cycle

- Morphological evaluation: CT - PET
  A CT- PET 6 months after initiation of treatment is MANDATORY, regardless of the number of courses received, to evaluate the primary endpoint criterion, unless progression before this point
- Quality of Life Questionnaire QLQ-C30 version 3.0
- Geriatric assessment for patients over 65 years:
  - ONCODAGE score (G8)
  - Charlson Index
  - Mini-Mental State Examination (MMSE)
  - Short version of the Geriatric Depression Scale - GDS 15 to be completed by the patient

Follow-up after discontinuation of treatment (for the three treatment arms)

After progression, patients will be followed up every 6 months until death:

- Clinical examination: weight, WHO and vital signs (temperature, pulse, blood pressure. This examination should be adapted to each patient, at the discretion of the investigator.
- Evaluation of persistent toxicity
- CT - PET
- QLQ-C30

EARLY DISCONTINUATION OF THE TREATMENT AND SUBSEQUENT TREATMENTS

- **Early discontinuation of treatment**

Patients may discontinue the treatment early for the following reasons:

- toxicity,
- disease progression,
- withdrawal of consent,
- lost to follow-up,
- patient refusal

Wherever possible, patients who discontinue the treatment early will be followed up on the same basis as other patients during treatment (every 8 weeks until progression).

- **2nd line**

A second line of treatment is possible for each treatment arm: in Arms A and B; patients can receive gemcitabine and in Arm C or can receive FOLFOX IV. The decision is left to the discretion of the investigator.

ANCILLARY STUDY LOGISTICS

For patients who have signed the biological informed consent form, a description of the ancillary biological study is given in Appendix 3 of this protocol.

Samples required
- **A blood sample consisting of 2 EDTA tubes of 5 (or 7) ml** will be collected before initiation of treatment (at the baseline assessment or before the 1st course).

Tubes are to be shipped, via the DHL box supplied at the opening of the centre, to:

Centre de Ressource Biologique EPIGENETEC
Unité INSERM UMR-S 1147 (ex 775)
45 rue des Sts Pères, 75006 PARIS
Headed by Professor Pierre Laurent-Puig

Only use the DHL box containing the DHL slip **for the INSERM UMR-S 1147 unit (ex 775).**

After sending the box, the box required for the next patient will be dispatched.

- Tumour block fixed in paraffin.

Blocks or slides are to be shipped, using the padded envelopes supplied at the opening of the centre, to:

Centre de Ressource Biologique EPIGENETEC
Unité INSERM UMR-S 1147 (ex 775)
45 rue des Sts Pères, 75006 PARIS
Headed by Professor Pierre Laurent-Puig

Only use the DHL box containing the DHL slip **for the INSERM UMR-S 1147 unit (ex 775).**

After sending the box, the box required for the next patient will be dispatched.

MANAGEMENT OF SERIOUS ADVERSE EVENTS (SAE)

Safety evaluation parameters
Safety will be evaluated by assessing the general and clinical condition of patients and by collecting data on events occurring between visits during consultations, and by carrying out regular blood tests. Toxicity will be evaluated using the NCI-CTCAE scale, version 4.0 (Appendix 6).
If any emergencies occur, the patient, his/her friends and family or family doctor should call the investigator to inform him/her of the event.

Definitions

a. Adverse event (AE)
An adverse event is a harmful medical occurrence in a biomedical research subject, whether or not it is related to the research or the investigational product.

All adverse events are to be reported in the case report form on the pages intended for that purpose.

b. Serious Adverse Event (SAE)
Is considered as a serious adverse event, any event that

- Causes death,
- Is life-threatening,
- Results in admission to hospital or extension of a hospital stay,
- Causes permanent disability or severe temporary disability,
- Causes a congenital anomaly/birth defect/abortion,
- Is medically significant (e.g. overdose, second cancer, and new developments considered as medically significant).

The terms 'disability' and 'incapacity' refer to any temporary or permanent physical or psychological disability that is clinically significant and has an impact on the physical activities and/or quality of life of the patient.

Any clinical event or laboratory result considered serious by the investigator and not meeting the severity criteria defined above is considered as medically significant. Such events may endanger the patient and require medical intervention to prevent an outcome that fulfils one of the severity criteria mentioned above (e.g.: overdoses, second cancer, pregnancies and new developments may be considered medically significant).

Pregnancy is an exclusion criteria in this study. However, if a pregnancy is discovered after inclusion, the female patient may be excluded from the study. The sponsor should be informed immediately using the form for reporting serious adverse events (no severity criteria will be ticked). The patient should then be monitored until the end of the pregnancy and the outcome of the pregnancy reported to the sponsor.

c. Adverse effect
Any untoward and unintended reaction to an investigational medicinal product, regardless of the dose administered or to any investigational item. The adverse effect is undesirable if it is subject to a severity criterion.

d. Unexpected Serious Adverse Effect
An unexpected serious adverse effect is an event that is not mentioned, or is different in nature, intensity, progression from that indicated in the Summary of Product Characteristics (or SmPCs)

e. New development
A new development may be: an unexpected frequency of an expected SAE, a SAE related to the trial procedure, insufficient efficacy in life-threatening diseases, clinical data.

f. Intensity (or severity)
An intensity criterion should not be confused with a severity criterion, which is used as a guideline to determine reporting obligations.

The intensity of the events will be estimated based on an extract of the CTC-AE classification version 4.0 (Appendix 6). The intensity of adverse events not listed in this classification will be assessed according to the following qualifiers:

- Mild (Grade 1): does not affect the patient's usual daily activities
- Moderate (Grade 2): disrupts the patient's usual daily activities
- Severe (Grade 3): prevents the patient from doing their usual daily activities
- Very Severe (Grade 4): requires resuscitation measures/ is life-threatening
- Death (Grade 5)

g. Causal relationship

- Related: an event is said to be related when a causal relationship can reasonably be suspected between the event and the investigational product
- Unrelated: an event is said to be unrelated when a causal relationship cannot reasonably be suspected between the event and the investigational product
- Doubtful: causality is described as “doubtful” when there are questions about the causal relationship between the event and the investigational product (the relationship cannot then be formally excluded or formally confirmed)

h. Sponsor liability

As soon as a serious adverse event report is received from the investigator, the sponsor should issue an opinion on the causal relationship between the serious adverse event and the investigational product(s).

If the serious adverse event is considered by the investigator and/or sponsor to be related to one of the investigational products (thus it is a serious adverse event), the expected or unexpected nature must be established.

If it is an unexpected serious adverse event, or if it is a new development, the sponsor must prepare an initial report to be sent to the ANSM, the Ethics Committee and the EMA (via EudraVigilance) within 7 days in the event of death or a life-threatening prognosis; in all other cases, it must be sent within 15 days.

If it is an expected adverse event, the event will be collated for inclusion in an annual safety report.

Non-serious events

Disease progression should not be considered as a SAE.

Events potentially related to progression but which could also be secondary to the treatment should continue to be reported (e.g. thromboembolic events, bleeding events, perforations, etc.)

Due to the severity of the disease in this study, some conditions determined as being SAEs are excluded from the SAE reporting procedure, namely:

Hospitalisation or surgery related specifically to treatment of the disease

Hospitalisation required to simplify study treatments or procedures

In this trial the reference documents are:

- For oxaliplatin, the Summary of Product Characteristics of Eloxatine® (Appendix 7)

- For 5-fluorouracil, the Summary of Product Characteristics of Fluorouracil Ebewe® 50 mg (Appendix 7)
- For folinic acid, the Summary of Product Characteristics of ELVORINE® (Appendix 7)
- For irinotecan, the Summary of Product Characteristics of Campto® (Appendix 7)
- For gemcitabine, the Summary of Product Characteristics of Gemzar® (Appendix 7)

The versions of the SmPCs used to determine the expected or unexpected nature of the event are those valid at the time of the analysis.

Action to take

The investigator shall notify the Sponsor of all Serious Adverse Events (expected and unexpected), whether or not they are attributable to the research, which have occurred during the study or within 30 days after the final administration of treatment.

All delayed Serious Adverse Events (i.e. occurring after this 30-day period) and reasonably considered to be related to the protocol treatment or research should be reported with no time limitations.

Reports are to faxed to **Centre de Randomisation Gestion Analyse (CRGA) at the FFCD** within 24 working hours using the "Serious Adverse Event Report" form (Appendix 10). The form must contain as much information as possible and be dated and signed. **Fax number: +33 (0)3 80 38 18 41.**

The investigator is responsible for the appropriate medical follow-up of patients until resolution or stabilisation of the effect or until the death of the patient. At times this can require lengthy follow-up that continues even after the patient had left the study.

The investigator forwards additional information to the sponsor using a SAE reporting form (ticking the Follow-up" box, to specify that it was a follow-up report and not an initial report) within 24 hours of receiving any such information. The investigator also forwards the last follow-up prior to the resolution or stabilisation of the SAE.
Investigators are required to respond to requests for additional information in order to document the initial observation.

STATISTICAL ANALYSIS

Planned study schedule

Number of centres: 60
Start of inclusions: December 2014
End of inclusions: December 2016
Analysis: June 2017

Calculation of the number of patients, statistical assumptions

In this trial, two new strategies are evaluated for the treatment of metastatic pancreatic adenocarcinoma.

The clinical assumptions retained are:
H_0: Rate of patients alive and progression-free at 6 month ≤ 30 % is unacceptable
H_1: Rate of patients alive and progression-free at 6 months >30 %, is beneficial. A 45% rate is expected.

Based on a Fleming's one-step plan (α=5 %, power = 90 %), 87 patients are to be randomised in each arm. Taking into account a 5% rate of lost to follow-up and non-evaluable, 92 patients will have to be randomised per arm, a total of **276 patients**.

The decision rules are as follows: out of 87 evaluable patients:

- If 33 patients or fewer are alive and progression-free at 6 months, the treatment will be considered as not effective.
- If 34 patients or more are alive and progression-free at 6 months, then the treatment will be considered as effective.

The decision rules will only apply to the FOLFIRINOX arm (arm B) with maintenance and to the FIRGEM arm (arm C); the FOLFIRINOX arm (arm A) is the control arm.

Statistical analysis:

All analyses will be performed as intention-to-treat (for all randomised patients regardless of inclusion/exclusion criteria).
The primary endpoint and safety analyses will be performed on the evaluable patient population defined as 'randomised patients who have received at least one treatment dose'.

General considerations:

For the description of the baseline population, analyses will be performed on the various treatment arms and on the entire population.
For efficacy and safety analyses, the analyses will be presented by treatment.

General statistics will be used to describe the variables, namely: for qualitative variables: frequencies and percentages and, for quantitative variables: mean, standard deviation, median, inter-quartile interval and range.

For the rate of patients alive and progression-free at 6 months, a 95% confidence interval will be calculated using the exact method (Newcombe, SIM 1998).

The Kaplan Meier (KM) method will be used to estimation survival rates and times. They will be described using medians and rates at different time points with a 95% confidence interval.

Median survival time will be calculated using a reverse "KM" method.

Safety will be evaluated by:

- Treatment duration, dose-intensity, and ratio between dose received/theoretic dose.
- Toxicity be described using NCI-CTC 4.0.
- Serious adverse events will be described.

Endpoint criteria

Primary efficacy outcome measure

Progression is defined as radiological progression according to RECIST v1.1. criteria and/or the clinical opinion of the investigator. Progression or death (of any cause) is taken into account if the event occurs during the first 6 months of treatment.

Secondary outcome measures

- Duration of disease control (see definition below)
- Progression-free survival is calculated as the time between the date of randomisation and the date of the first progression (local or metastatic) or clinical progression, date of death (of any cause). Patients who are progression-free and still living were censored on the date of last receiving news.
- Overall survival is calculated as the time between the date of randomisation and the date of death (of any cause). Patients who are alive will be censored on the date of last receiving news.
- Time to progression during maintenance is defined as the time between the end of induction treatment (FOLFIRINOX or FOLFIRI3) and the date of radiological progression during the maintenance period.
- The duration of maintenance treatment (arm B) will be calculated as the time between the last FOLFIRINOX course and the date of progression resulting in the resumption of FOLFIRINOX.
- Efficacy will be evaluated using the objective response rate according to RECIST 1.1 criteria at 2, 4 and 6 months.
- Best response to treatment during the first 6 months will be derived.
- The frequency of using haematopoietic growth factors for haematological toxicity will be described.
- Percentage of patients receiving a 2nd line therapy will be described
- Quality of life (QLQ-C30 EORTC v3.0 questionnaire) will be studied descriptively. Time to deterioration of quality of life will be analysed.
- Tolerance will be described using NCI-CTC grades, Version 4.0. Close attention will be paid to neurotoxicity

In arm A (Folfirinox), duration of disease control is defined as the period of time between the randomisation date and the date of progression under treatment (clinical and/or radiological) or death (for any reason and at any time) or the date of switching lines.

In arm B with maintenance (arm B), duration of disease control is defined as follows:

- After progression during maintenance with LV5FU2 (PFS1), if the disease is not controlled after reintroduction of FOLFIRINOX (PFS2) then the duration of disease control is equal to the period of time between randomisation and progression before the reintroduction of FOLFIRINOX (PFS1).
- After progression during maintenance with LV5FU2 (PFS1), if the disease is not controlled after reintroduction of FOLFIRINOX then the duration of disease control is equal to the period of time between randomisation and progression (PFS2) with FOLFIRINOX (PFS1 + PFS2).

In the FIRGEM arm (arm C), duration of disease control is defined as follows:
If discontinuation of alternate treatments (FOLFIRI.3/Gemcitabine) is due to progression (PFS1) then:

- If the disease is not controlled after changing the treatment then the duration of disease control is equal to the period of time between randomisation and progression before changing the treatment (PFS1).
- If the disease is again controlled after changing the treatment, then the duration of disease control (stability, OR) is equal to the period of time between randomisation and progression (PFS2) with the treatment (PFS1 + PFS2)

If the alternation of treatments is discontinued for a reason other than progression (e.g. toxicity, decision of the investigator, etc.), then the duration of disease control will be the period of time up to the first progression (PFS1).

Event-free patients will be censored on the date of last radiological evaluation or on the cut-off date.

STUDY COMMITTEES

Independent committee

An independent committee will be set up and will include at least three gastro-oncologists, a statistician/methodologist, and a pharmacovigilance officer. The independent committee will be contacted at any time during the protocol, whenever deemed necessary by the Sponsor.

Steering committee

A steering committee will be set up. The chairman of the steering committee will act as the study coordinator. This committee will also include the co-coordinators, the FFCD project manager for the study, the FFCD statistician, and the chairman of the Biological Research Committee. Its tasks will include taking research management decisions (amendment, early closure if necessary, etc.). This committee will meet as many time as necessary throughout the study. The steering committee will take all the necessary decisions about substantial amendments to the protocol, and the closure or extension of the study.

Medical review

A medical review will be set up to check the quality of the clinical data collected. In the event of discrepancy between the data entered by the investigator and the medical review data, the data manager will send a request for clarification to the investigator.

Biological research committee

A Biological Research Committee will be established and its remit is to manage any problems encountered with the collection and banking of samples, as well as the organisation of the testing of samples. The committee will meet regularly and report on its proposals to the Steering Committee. This committee includes the study coordinator and a biologist; Professor Pierre Laurent Puig acts as the chairman of the committee.

BASIS AND RATIONALE OF THE STUDY

The incidence of pancreatic ductal adenocarcinoma is steadily increasing in most Western countries: in 2012 in France, 11662 new cases were reported (compared to 4887 in 2000), meaning that the incidence has more than doubled in 12 years. Mortality is closely related to incidence and it is the fourth highest cause of death [1]. For all stages of the disease, 5-year survival rates do not exceed 5% [2].
At the time of diagnosis, 50-60% of cases of pancreatic cancer have already reached the stage of visceral metastases. In addition, out of the 10-20% of patients able to benefit from curative resection, most will relapse, despite the advances in post-operative adjuvant chemotherapy (based on FU-folinic acid or gemcitabine) which has increased the survival rate after 5 years from 10 to 20% [3, 4, 5, 6].

At a metastatic stage, pancreatic adenocarcinoma remains an incurable disease, associated with a median survival of 2 to 4 months without chemotherapy. Gemcitabine monotherapy offered the first glimmer of hope [7]; however, it was not until 2011, after 13 years of negative phase III studies, that major progress was achieved in the management of such pancreatic patients. A combination with FOLFIRINOX [8] allowed, in patients in good health at a metastatic stage with normal bilirubinaemia and under the age of 76 years, to increase their overall survival (from 6.8 to 11.1 months - $p<0.0001$) and progression-free survival (from 3.3 to 6.4 months – $p<0.0001$) compared to gemcitabine. The main toxicity of the treatment are haematological and gastrointestinal, related to the onset of reversible sensory neuropathy, in relation to oxaliplatin.
According to INVS (French Institute for Public Health Surveillance) data, pancreatic-cancer patients in France under the age of 76 years (thus potentially eligible for a FOLFIRINOX regimen) account for 58% of cases. Of this number, half are aged under the age of 65 years and the other half are aged between 65 and 75 years [9].
Due to increased life expectancy at birth (85 years for women, 78 years for men), the proportion of people over the age of 65 with pancreatic cancer is gradually increasing. In the study from T. Conroy et al, the median age of patients at baseline was 61 years and FOLFIRINOX chemotherapy remained beneficial in patients over 65 years of age [8]. A geriatric evaluation is used to identify the frailty of patients by assessing autonomy and social environment as well as screening for walking disorders, cognitive disorders, mood disorders and malnutrition. [10]. Geriatric evaluation parameters are correlated with treatment tolerance and overall survival of elderly patients treated for cancer of the colon, oesophagus or ovaries [11, 12]. No specific data exists for pancreatic cancer in elderly subjects.

It would be worthwhile investigating in older patients eligible for FOLFIRINOX whether geriatric frailty factors are predictive of treatment failure in order to better target the indications.

FIRGEM is an original sequential treatment strategy [13]. This novel therapeutic approach allows patients to be administered 3 cytotoxic drugs (5FU, irinotecan and gemcitabine), with no known cross-resistance to each other, sequentially, which limits cumulative or non-cumulative toxicity and can preserve the patient's quality of life. In a randomised phase II study, patients received either FOLFIRI.3 alternately every 2 months with gemcitabine (FIRGEM strategy) or gemcitabine alone, continuously. The FOLFIRI 3 regimen consisted of administering 50% of the dose of irinotecan before the continuous 5FU and 50% at the end of the infusion of the continuous 5FU, to optimise the reciprocal modulations exerted by 5FU and irinotecan [14]. Overall survival was 11 months in the FIRGEM arm and 8.2 months in the control arm. The rate of progression-free survival after 6 months was 45% in the FIRGEM arm, extremely close to the numbers reported with FOLFIRINOX. Haematological and gastrointestinal toxicity were similar to those reported with FOLFIRINOX; however, this strategy does not induce limiting neurotoxicity and allows oxaliplatin to be used in second line. [13]

To improve tolerance and efficacy of first-line chemotherapy in metastatic pancreatic adenocarcinoma, two attitudes can be evaluated:

- A stop-and-go strategy, as in OPTIMOX-1 for metastatic colorectal cancer [15]: treatment with FOLFIRINOX and LV5FU2 as maintenance. FOLFIRINOX with LV5FU2 as maintenance has never been evaluated in pancreatic adenocarcinoma. This strategy, which is used in colorectal cancer, could improve the tolerance of FOLFIRINOX without reducing its efficacy.

- A sequential strategy (the “FIRGEM” regimen) alternating FOLFIRI.3 with gemcitabine.

Only one previous strategic phase III trial evaluating a second line of treatment exists [16].

The objective of this three-arm randomised study is to evaluate standard treatment with FOLFIRINOX (until disease progression or unacceptable toxicity), FOLFIRINOX with LV5FU2 maintenance (in patients whose disease is controlled after 4 months, 8 courses) and treatment with FIRGEM.
This 3-arm Phase II study could be used to design an extensive Phase II strategic study on maintenance or sequential strategies.

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ADMINISTRATIVE CONSIDERATIONS

STUDY SPONSOR

The study sponsor is Fédération Francophone de Cancérologie Digestive (FFCD). The study was registered under EudraCT number 2014-002574-36.

REMINDER OF TEXTS IN FORCE

This study will be conducted according to the French law in force, in accordance with the ethical principles of the Helsinki Declaration of 1964 revised in Edinburgh in 2000, the Good Clinical Practices of the International Harmonization Conference (ICH–E6, 17/07/96), the European Directive (2001/20/EC) on the conduct of clinical trials, the amended Huriet law (20/12/98) relating to the Protection of Persons Involved in Biomedical Research as well as the provisions stipulated by the French data protection agency (CNIL) (Law No. 94-548 of 1/07/94 supplementing Law No. 78-17 of 6/01/78).

CIVIL LIABILITY INSURANCE

The sponsor has taken out insurance to cover its civil liability (number 137681 dated 09/05/2014), in compliance with Article L 1121-10 of the French public health code (Appendix 12).

REQUEST FOR AUTHORISATION FROM THE EC AND ANSM

This protocol has been approved by the EC (Ethics Committee) of SUD MEDITERRANEE II on 11/07/2014 (Appendix 13).
This protocol was authorised by the ANSM (French National Agency for Medicines and Health Products Safety) on 20/08/2014 (Appendix 14).

COLLECTING THE CONSENT OF PATIENTS

The investigator undertakes to collect, after providing information, the clinical and biological consents of the patient in writing (patient information leaflets and consent forms in Appendices 1 and 2) before the patient is enrolled in the study. The investigator must retain a duplicate copy of the consent documents for 15 years, to be shown to the supervisory authorities during any inspections. An original copy should be given to the patient.

In accordance with the recommendations of the Cancer Plan (Measure 4.3.), this document has been submitted for review, advice and guidance to the Patient Committee for Clinical Research (CPRC) of the French League Against Cancer.

INFORMATION FOR HOSPITAL MANAGEMENT AND RESEARCH AGREEMENT

Before setting up the study, the hospital management will be informed by the sponsor of the investigator's interest in participating in this study.

A research agreement will be drawn up at no additional cost between the administrator of the investigating centre and the sponsor.

DATA ARCHIVING

Records shall remain confidential and may only be consulted under the responsibility of the doctors taking care of the patients. During any inspections, the sponsor and the health authorities will have direct access to the documents.
At the end of the study, the investigator will retain the case report form for 15 years.

IT MEDIA

In accordance with the text of Law No. 78-17 of 6 January 1978, as amended by the Law of 9 August 2004, relating to data processing, files and civil liberties, data from the study will be recorded in a computer database at the Centre de Randomisation et de Gestion Analyse of the FFCD. No elements revealing the identity of patients will be included.

DATA PROCESSING

Centre de Randomisation, de Gestion et d'Analyse (CRGA) of the FFCD is responsible for the management and analysis of data.

MONITORING, QUALITY ASSURANCE AND INSPECTIONS BY THE AUTHORITIES

The investigator agrees in advance that the records of patients enrolled will be consulted by a person mandated by the Sponsor and/or the health authorities to conduct an audit. On-site visits to view the files, scheduled after agreement of the investigator, may take place during or after the trial enrolment period.
This protocol will be monitored by the mobile CRAs of the FFCD.

PUBLICATION RULES

Publication rules shall comply with those established by the PRODIGE group (Appendix 11).

APPENDICES