PRODIGE 37 (FFCD 1406) FIRGEMAX

MULTICENTER RANDOMISED PHASE II TRIAL ASSESSING NAB-PACLITAXEL + GEMCITABINE/FOLFIRI.3 VERSUS NAB-PACLITAXEL + GEMCITABINE AS A SEQUENTIAL FIRST-LINE TREATMENT OF METASTATIC PANCREATIC CANCER

Phase II randomised - multicenter

EudraCT n° 2014-004449-28

FFCD – UNICANCER GI - GERCOR Intergroup Trial

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LIST OF ABBREVIATIONS

AE	Adverse event
ALAT	Alanine aminotransferase (or SGPT: Serum Glutamic-Pyruvic Transaminase)
ANC	Absolute Neutrophil count
ANSM	French National Agency for Medicines and Health Products Safety
ASAT	Aspartate-aminotransferase (or SGOT: serum glutamic oxaloacetic transaminase)
CEA	Carcinoembryonic antigen
CI	Contraindication
CR	Complete Response
CRA	Clinical Research Associate
CT	Chemotherapy
CT-scan	X-ray computed tomography
CTC	Common Toxicity Criteria
EC	Ethics committee
EDTA	Ethylenediaminetetraacetic acid
EGF	Epidermal Growth Factor
EGFR	Epidermal Growth Factor Receptor
5FU	5-fluorouracile
FBC	Full Blood Count
FFCD	French Federation of Digestive Oncology
FOLFIRI	Folinic acid - Fluorouracile – Irinotecan
GGT	Gamma glutamyl transpeptidase
Hb	Haemoglobin
HBP	High blood pressure
HR	Hazard ratio
INR	International Normalised Ratio
IRM	Magnetic resonance imaging
ITT	Intention to treat
IV	Intravenous
D	Day
KM	Kaplan Meier
LDH	Lactate dehydrogenase
LLN	Lower Limit of Normal
MDRD	Modification of the Diet in Renal Disease
mTNS	Modified Total Neuropathy Score
N	Normal
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
OS	Overall Survival
OR	Objective Response
PAL	Alkaline phosphatase
PFS	Progression-free survival
PR	Partial Response
PT	Prothrombin Time
Q1-Q3	Quartiles
RECIST	Response Evaluation Criteria In Solid Tumours
SAE	Serious adverse event
SD	Stability (stable disease)
CAP	Chest-abdomen-pelvis
UICC	Union for International Cancer Control
WHO	World Health Organisation

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PROTOCOL ACCEPTANCE FORM

ETUDE PRODIGE 37- FFCD 1406 – FIRGEMAX

Multicenter randomised phase II trial assessing nab-paclitaxel + gemcitabine/folfiri.3 versus nab-paclitaxel + gemcitabine as a sequential first-line treatment of metastatic pancreatic cancer

EudraCT n° 2014-004449-28

Version 1.1 –8.12.2014

This version of the protocol is approved by:

For the sponsor: Mme Cécile GIRAULT Date: 08.12.2014 Signature:

For the Coordinator: Pr Julien TAIEB Date: 08.12.2014 Signature:

I the undersigned, Doctor: .....

Having reviewed the prerequisites of this research, the Protocol and its Appendices, certify that I conduct this trial in accordance with Good Clinical Practice and in accordance with the applicable provisions of the Code of Public Health.

I undertake in particular:

- to respect the protocol as well as any changes notified by the Sponsor,
- to agree to supervise research in the centre and to train my colleagues in conducting research and to supply a nominative list of my colleagues,
- in the case of patients lost to follow-up, to request information on the patients condition from their home town mairies at the time of analysis or when the Sponsor requests it,
- to have each patient sign a written consent after making them aware of the information sheet intended for them and this before any research act,
- to report serious adverse events or developments within 24 hours after having become aware of them, in accordance with protocol indications,
- to respect the criteria for inclusion and non-inclusion, as well as the start and end dates of the study,
- to participate in the biological part of the study and to dispatch the samples as recommended,
- to complete all items of the CRF (case report form), monitor the quality of data collection, and good product management,
- to archive and keep documents related to the trial for a period of 15 years after the end of the study,
- to inform the Sponsor of all conflict of interest situations likely to impair my scientific independence in relation to the research,
- to immediately inform the Sponsor of any cordial or contentious action exerted by a person undergoing the research or their dependents which may invoke the responsibility of the Sponsor,
- to accept the periodic visits of the Sponsor's representatives, provide them with all research-related source documents and material, to ensure quality control of the data recorded in the case report form. Accept a form of audit control from the Sponsor and/or inspection by the health authorities,
- to respond by telephone or email to requests for corrections or clarifications on the case report form,
- to allocate adequate time to the FFCD CRA for the signing of forms, response to questions and actions to be taken.

Date: Signature:

SEAL:

Address the original to the CRGA of the FFCD – 7 bd Jeanne d'Arc – BP 87900 – 21079 Dijon Cedex

SYNOPSIS

Title	**PRODIGE 37 - FIRGEMAX** **Multicenter randomised phase II trial assessing nab-paclitaxel + gemcitabine/folfiri.3 versus nab-paclitaxel + gemcitabine as a sequential first-line treatment of metastatic pancreatic cancer**
Sponsor	French Federation of Digestive Oncology (FFCD)
Design	Multicenter Randomised Open Phase II Study
Study objectives	**Main objective:** The main objective of Phase II is to assess the rate of patients alive with no radiographic (RECIST V1.1) and/or clinical progression at 6 months in each arm **Secondary objectives:** - Overall survival - Objective response rate - Progression-free survival - Time to treatment discontinuation - Toxicities according to the NCI CTC v4.0 - Peripheral neuropathic toxicities according to the mTNS simplified scale (Modified Total Neuropathy Score of GOG-Taxane scores) - Quality of life (EORTC QLQ-C30 questionnaire)
Inclusion Criteria	- Histological or cytological confirmation of pancreatic adenocarcinoma (in primary tumour or metastatic lesion) - Distant metastatic disease - Scan (or MRI if scanner contraindicated) completed within 3 weeks of the start of treatment - At least one lesion measurable by RECIST v1.1 - Life expectancy> 3 months - No previous chemotherapy (adjuvant chemotherapy with gemcitabine authorised if administered more than 6 months prior to enrolment) - No previous radiotherapy (unless at least one measurable target lesion outside of the irradiation zone) - Pain must be monitored before inclusion - 18 years $\leq$ age $\leq$ 75 years - Performance status: WHO $\leq$ 2 - ANC $\geq$ 1500/mm^3, platelets $\geq$ 100 000/mm^3, haemoglobin $\geq$ 9 g/dL - ASAT (SGOT), ALAT (SGPT) $\leq$ 2.5 x ULN or $\leq$ 5 x ULN if liver metastases found - Bilirubin $\leq$ 1.5 x ULN (patients drained using the retrograde technique are includable), creatinine $\leq$ 120 µmol/L, or MDRD creatinine clearance $\geq$ 60 mL/min - Women of childbearing age must have a negative pregnancy test (β HCG) before starting treatment - Women of childbearing age as well as men (who have sexual relations with women of childbearing age) must agree to use effective contraception without interruption for the duration of treatment and 6 months after administration of the last treatment dose - Patient affiliated to the social security scheme - Patient information and signature of informed consent
Exclusion Criteria	- Other types of pancreatic tumours, especially endocrine or acinar cell tumours - Ampulloma - Presence of meningeal or cerebral metastases, bone metastases - Gilbert's syndrome - Presence of neuropathy> grade 1 according to NCIC-CTC 4.0 - Contraindications specific to the studied treatments - History of chronic diarrhoea or inflammatory disease of the colon or rectum, or of unresolved occlusion or sub-occlusion for which symptomatic treatment is being administered - Other concomitant cancer or history of cancer during the 5 years, with the exception of carcinoma *in situ* of the cervix or basal cell or squamous cell carcinoma, considered cured - Significant history of heart or respiratory disease, including any history of interstitial pneumonia - Patient already included in another clinical trial with an experimental molecule

	- Women who are breast-feeding - Persons deprived of liberty or under guardianship - Unable to submit to medical monitoring during the trial due to geographical, social or psychological reasons
Treatment plan	**Arm A (experimental arm): Alternating 2 months of nab-Paclitaxel + gemcitabine with 2 months of FOLFIRI.3** Nab-Paclitaxel + gemcitabine (3 wks/4 for 2 months) • Nab-Paclitaxel = 125 mg/m² • Gemcitabine = 1000 mg/m² in IV 30 minutes On D1, D8, D15 and D29, D36, D43 Then • FOLFIRI.3 (a course every 14 days for 2 months) Irinotecan 90 mg/m² on D1 in 60 min Y port infusion of folinic acid, Folinic acid 400 mg/m² (or 200 mg/m² Elvorine) on D1 as a 2 hour infusion, continuous 5FU 2000 mg/m² for 46 hours, Back to irinotecan 90 mg/m² (1hr) from D3 to the end of the 5FU infusion On D1, D15, D29 and D43 The sequence will be repeated until disease progression or unacceptable toxicity. **Arm B (reference arm): nab-Paclitaxel + gemcitabine** Nab-Paclitaxel + gemcitabine (3 wks/4) Nab-Paclitaxel • = 125 mg/m • Gemcitabine = 1000 mg/m² IV 30 minutes On D1, D8, D15 and D29, D36, D43 - The treatment will be repeated until disease progression or unacceptable toxicity.
Randomisation	Randomisation (1:1) of patients will be carried out according to the minimisation technique and will be stratified according to the following stratification factors: - Centre - WHO: 0 vs. 1 vs. 2 - Metastatic site: 1 vs. > 1
Calculation of the sample size	Binomial Method The hypotheses for the calculation of the required number of subjects are: H_0: rate of patients alive without a progression of 40 % at 6 months is insufficient. H_1: rate of patients alive without progression of over 40% at 6 months is hoped for. A rate of 60% is expected By using the exact binomial method, an alpha one-sided risk of error of 5% and a power of 90%, it is necessary to include 56 patients per arm. The decision rules only apply to the experimental arm. At the end of recruitment, during the analysis: - If 27 patients or less are alive without progression the treatment is judged ineffective. - If 28 patients or more are alive without progression we reject H_0 and conclude that the treatment is effective. Assuming a rate of patients lost to follow-up or not evaluable at 10%, it is necessary to include 62 patients per arm or **124 patients in all.**
Statistical Analysis	Analysis of the primary endpoint will be by intention to treat (ITT) modified with all evaluable patients included in the study regardless of eligibility criteria and the treatment received. The descriptive analysis will be carried out in strict ITT. The tolerance analysis will be performed on all patients who received at least one treatment dose during the study. A statistical analysis plan (SAP) will be drafted before the base gel.
Ancillary study	A biological study will assess: - The constitutional genetic polymorphisms that may influence the efficacy and tolerance of chemotherapy molecules (UGT1A1, ERCC1, MTHFR, DPD, TS...). - A study of sections in paraffin in search of immunohistochemical biomarkers predictive of treatment response
Number of patients	124 patients
Duration of inclusion and participation of each patient	Rhythm of theoretical inclusions: 5 patients per month Number of centres: 20 centres Start of inclusions: April 2015 End of inclusions: 24 months after the start of the inclusions or April 2017. First analyses: October 2017

TREATMENT MONITORING AND EXAMINATION SCHEDULE

	BEFORE TREATMENT	DURING TREATMENT and in case of stopping treatment without progression (e.g. toxicity or patient refusal)		AFTER STOPPING TREATMENT for progression (failed strategies)
	In the 7 days preceding the start of treatment (excluding CT-scan)	Before each administration of treatment	Every 8 weeks and 30 days after the date of last administration of CT regardless of the arms	Every 2-3 months until death
Signed Informed clinical and biological Consent	X			
CLINICAL EXAMINATION				
Weight, body surface	X	X	X	X
Height	X			
WHO performance status	X	X	X	X
Evaluation of toxicities NCI-CTCAE version 4.0		X	X	X (tox. persistent)
Evaluation of peripheral sensory neuropathies (v4.0)	X	X	X	X
Evaluation of neurotoxicity's simplified mTNS scale	X		X	X (2 months after stopping ttt)
QLQ-C30	X	X (every month for the first 4 months)	X (every month for the first 4 months)	X
Morphine treatment and pain assessment (VAS)	X	X	X	
BIOLOGICAL TESTS				
Biological test	X*	X***	X*	
Pregnancy test	X		X and within 30 days after stopping treatment	
CA19 -9 and CEA Markers	X		X	
PARACLINICAL EXAMS				
Chest-abdomen-pelvis CT-Scan or MRI	X**		X	X
ECG	X**			
ANCILLARY BIOLOGICAL STUDY				
2 EDTA tubes 5 or 7 mL of blood	X			
Biopsies or tumour block, fixed in paraffin	X			

*: FBC, platelets, PT, sodium, potassium, calcium, bilirubin (total, free and conjugated), ALAT, ASAT, Alkaline phosphatase, LDH, serum Creatinine, creatine clearance de la (MDRD), albuminemia

**: In the 3 weeks preceding inclusion

***: FBC, platelets, bilirubin (total, free and conjugated), serum creatinine, sodium, potassium

1. Study objectives

1.1 Main objective

The main objective is to evaluate the rate of patients alive and with no radiographic (RECIST V1.1) and/or clinical progression at 6 months in each arm.

Clinical progression is defined as a worsening of the general condition not related to treatment, tumour mass palpable on clinical examination (lymphadenopathies, tumour hepatomegaly, peritoneal carcinomatosis), pleural effusion or ascites

1.2 Secondary objectives

- Overall survival
- Objective response rate by RECIST v1.1
- Progression-free survival
- Time to treatment discontinuation
- Toxicities according to NCI CTC v4.0
- Peripheral neuropathic toxicities according to the mTNS simplified scale (Modified Total Neuropathy Score)
- Quality of life (EORTC QLQ-C30) questionnaire

A biological study will assess:
- The constitutional genetic polymorphisms may influence the efficacy and tolerance of chemotherapy molecules (UGT1A1, ERCC1, MTHFR, DPD, TS...).
- A study in paraffin sections in search of immunohistochemical biomarkers predictive of treatment response

2. Selection of patients at registration

2.1 Inclusion criteria

- Histological or cytological confirmation of pancreatic adenocarcinoma
- Distant metastatic disease
- Scan (or MRI if scanner contraindicated) completed within 3 weeks of the start of treatment
- At least one lesion measurable by RECIST v1.1 criteria
- Life expectancy> 3 months
- No previous chemotherapy (adjuvant chemotherapy with gemcitabine authorised if administered more than 6 months prior to inclusion)
- No previous radiotherapy (unless at least one measurable target lesion outside the irradiation zone)
- Pain must be monitored before inclusion
- 18 years < age < 75
- Performance status: WHO < 2
- ANC ≥ 1500/mm3, platelets ≥ 100 000/mm3, haemoglobin ≥ 9 g/dL
- ASAT (SGOT), ALAT (SGPT) ≤ 2.5 x ULN or ≤ 5 x ULN if liver metastases found
- Bilirubin ≤ 1.5 x ULN (patients drained by retrograde technique are includable), creatinine < 120 µmol/L, or MDRD creatinine clearance > 60 mL/min
- Women of childbearing age must have a negative pregnancy test (β HCG) before starting treatment
- Women of childbearing age as well as men (who have sexual intercourse with women of childbearing age) must agree to use effective contraception without interruption for the duration of treatment and 6 months after the administration of the last treatment dose
- Patient affiliated to the social security scheme
- Patient information and signature of informed consent

2.2 Non-inclusion criteria

- Other types of pancreatic tumours, especially endocrine or acinar cell tumours
- Ampulloma
- Presence of meningeal or cerebral metastases, bone metastases
- Gilbert's syndrome
- Presence of neuropathy> grade 1 according to NCIC-CTC 4.0
- Contraindications specific to the studied treatments
- History of chronic diarrhoea or inflammatory disease of the colon or rectum, or of unresolved occlusion or sub-occlusion for which symptomatic treatment is being administered
- Other concomitant cancer or history of cancer during the 5 years, with the exception of a *carcinoma in situ* of the cervix or basal cell or squamous cell carcinoma, considered cured
- Significant history of heart or respiratory disease, including any history of interstitial pneumonia
- Patient already included in another clinical trial with an experimental molecule
- Women who are breast-feeding
- Persons deprived of liberty or under guardianship
- Unable to submit to medical monitoring during the trial due to geographical, social or psychological reasons

3. INCLUSION RESULTS

Inclusion results should be carried out in the 8 days prior to starting treatment, except for the paraclinical tests that can be carried out within 3 weeks prior to randomisation.

Clinical tests:

- Measurement of weight, height and body surface
- General condition according to the WHO scale
- Evaluation of the peripheral neurological symptoms according to the mTNS simplified scale and NCI CTC v4.0
- Pain assessment by VAS (patient expresses the degree of pain they feel on a scale of 0 to10 (0 being "no pain" and 10 being "worst imaginable pain")
- Morphine treatment: dose, type

Biological tests dated less than 7 days:

- FBC, platelets, PT, sodium, potassium, calcium
- Total bilirubin, free and conjugated, ALAT, ASAT, alkaline phosphatases, LDH
- Serum creatinine, creatinine clearance (MDRD – Appendix 4)
- Serum albumin
- Markers: CA 19-9, CEA
- Pregnancy test for women of childbearing age

Quality of life questionnaire:

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

Morphological and paraclinical examinations **in the three weeks prior to inclusion**:

- Chest-abdomen-pelvis CT (CAP CT-scan or MRI scan if contraindicated) ECG

Ancillary biological study (Appendix 3 and chapter 8):

- Sampling of 2 EDTA tubes of 5 or 7 ml of blood before the first treatment. The justification and logistics of this study are described jointly in Appendix 3 and Chapter 8.

4. RANDOMISATION

Following signing of the consent form and validation of the results of the initial inclusion review, eligible patients will be randomised by the **Center for Randomisation - Management - Analysis (CRGA) of the FFCD**.

The investigator must fax the completed and signed randomisation sheet to the CRGA of the FFCD:

Monday to Friday from 9am to 6pm

Fax: + 33 (0) 3 80 38 18 41 / Tel: + 33 (0) 3 80 66 80 13

A registration confirmation will be faxed back to the investigator and pharmacist with the patient's registration number and the arm assigned by randomisation.

After randomisation of the patient in the study, treatment should begin as soon as possible and within a maximum period of 14 days.

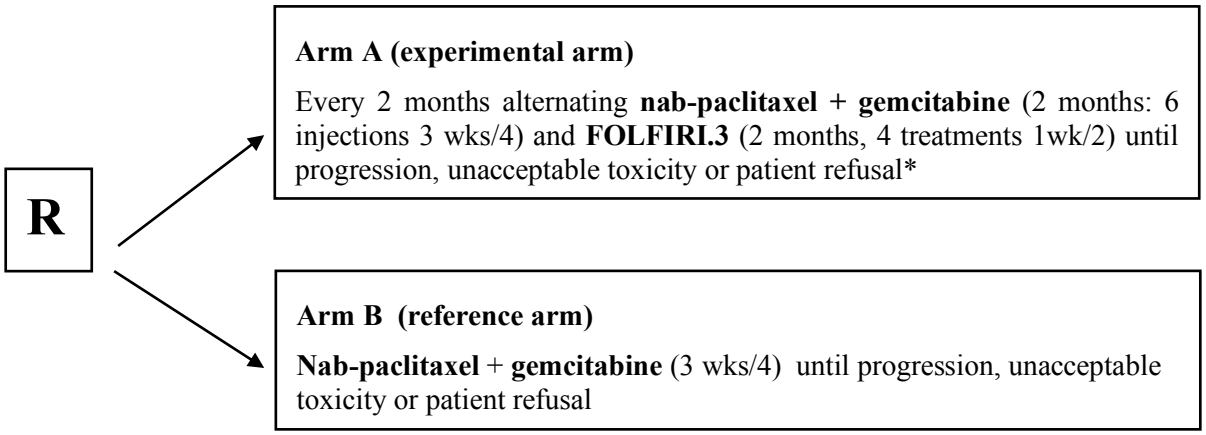
A case report will be sent at the opening of the centre. A new case report will then be sent after each randomised patient

Stratification

The randomisation (1:1) of patients will be conducted by minimisation and will be carried out according to the following stratification factors:

- Centre
- WHO: 0 vs. 1 vs. 2
- Metastatic site: 1 vs. > 1

5. STUDY DESIGN



* If progressive, limiting toxicity with one of the 2 treatments, continuation of the other treatment until progression, unacceptable toxicity or patient refusal

6. TREATMENT

6.1 ALTERNATING NAB-PACLITAXEL/GEMCITABINE AND FOLFIRI.3 (Arm A)

Every 2 months alternating nab-paclitaxel/gemcitabine and FOLFIRI.3

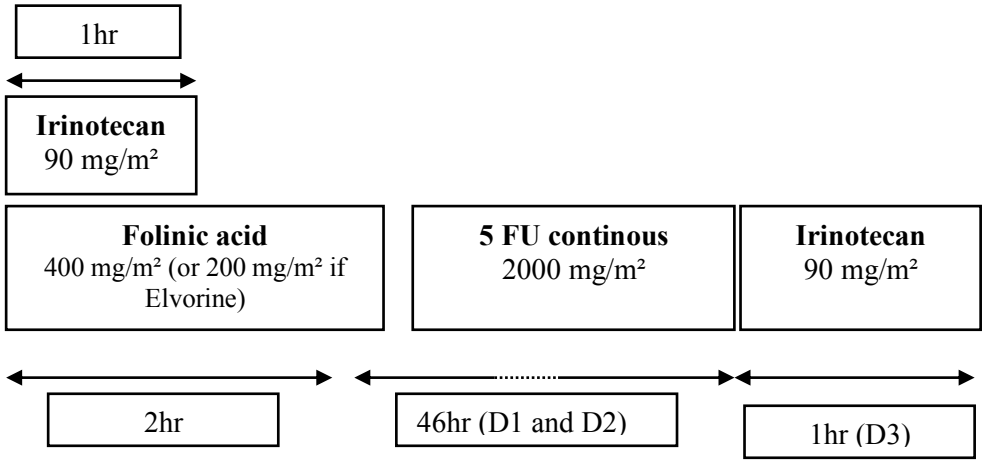
<u>NAB-PACLITAXEL + GEMCITABINE</u>
3 weeks out of 4, an injection on D1, D8, D15 and D29, D36 and D43 (2 month treatment).

- Nab-paclitaxel: 125 mg/m² of nab-paclitaxel by 30 min infusion

- Gemcitabine 1000 mg/m² infusion over 30 min immediately after the end of the nab-paclitaxel infusion

FOLFIRI.3:
1 week out of 2, or an injection on D1, D15, D29, D43 - or 2 months of treatment.

- Irinotecan 90 mg/m² on day 1 60 min Y infusion of folinic acid
- Folinic acid 400 mg/m² (or 200 mg/m² Elvorine) on D1 as a 2 hour infusion
- 5FU continuous 2000 mg/m² for 46 hours
- Then back to irinotecan - 90 mg/m² in 60 min infusion on day 3, at the end of the 5FU infusion



In case of progression, limiting toxicity with one of the two treatments it is recommended (except against-indication or rejection) to continue the other treatment until progression, unacceptable toxicity or patient refusal.

6.2 NAB-PACLITAXEL + GEMCITABINE (Arm B)

3 weeks out of 4, or an injection on D1, D8, D15 and resumption on D29 (for each treatment, D1 = D29).

- Nab-paclitaxel: 125 mg/m² by infusion of nab-paclitaxel over 30 min
- Gemcitabine 1000 mg/m² by infusion over 30 min immediately after the end of the nab-paclitaxel infusion

7. DOSE ADAPTATION ACCORDING TO THE TOXICITIES

Toxicities requiring dosage adjustment will be evaluated according to the NCI-CTCAE v4.0 scale (Appendix 7).

7.1 Criteria required before completion of any new course of treatment

Criteria required before completion of any new course of treatment:

- ANC $\geq$ 1500/mm^3
- Platelets $\geq$ 100 000/mm^3
- Gastrointestinal toxicities $\leq$ grade 1

As long as these criteria have not been met, symptomatic treatment should be optimised and an FBC will be conducted every 7 days until obtaining the required figures. The treatment can then be carried out.

In addition to these criteria:

- treatment by FOLFIRI.3 may only be administered if serum bilirubin< 1.5 times the normal.
- gemcitabine may be administered if the transaminases are< 5 times the normal.

Otherwise, a biological control shall be performed every 7 days until obtaining the required figure; administration of FOLFIRI.3 can then be conducted.

As long as these criteria are not met, the treatment should be postponed for a week.
If over 21 days of treatment deferral after the last administration, the patient will stop the treatment under study and will continue to be monitored as part of the protocol.

7.2 Dosage adjustment based on toxicities observed during the intercure period

Depending on the maximum grade of toxicity observed during the intercure period, dosage adjustments will be required according to the below table.

Treatment will only begin when the criteria required before completion of any new treatment is obtained (see section 7.1).

The occurrence of a grade 4 toxicity (excluding haematological toxicities or other manageable toxicity) will impose the permanent cessation of the study treatment. Secondary treatments will be at the discretion of the investigator. In all cases, the patient will continue to be monitored as part of the protocol and according to the protocol rythym.

The occurrence of febrile neutropenia, peripheral neuropathy or pulmonary embolism is the subject of a separate paragraph (see paragraphs 7.3, 7.4 and7.5).

Table n°1: Haematological toxicity or not: dose adaptation of the various treatments

<table>
<tr><td rowspan="2">Toxicity/Grade CTCAE v4.0</td><td rowspan="2">1</td><td rowspan="2">2</td><td colspan="2">3-4</td></tr>
<tr><td>FOLFIRI.3</td><td>Gemcitabine + Nab-Paclitaxel</td></tr>
<tr><td>Anaemia</td><td>No modification</td><td>No modification, transfusion support to be discussed</td><td colspan="2">No modification,
transfusion support mandatory</td></tr>
<tr><td rowspan="2">Neutropenia,

Thrombopenia</td><td rowspan="2">No modification</td><td rowspan="2">No modification if administration within a period of 14D[1]
Administration of G-CSF[4] to be discussed</td><td>- 5FU 1600 mg/m² (46h)
- Irinotecan 80 mg/m² (J1-J3)</td><td>- Gemcitabine 800 g/m²
- Nab-Paclitaxel[3] 100 mg/m²</td></tr>
<tr><td colspan="2">If neutropenia, administration of G-CSF[4] required.</td></tr>
<tr><td>Toxicity/Grade CTCAE v4.0</td><td>1</td><td>2</td><td colspan="2">3</td></tr>
<tr><td>Diarrhoea</td><td>No modification</td><td>No modification if administration within a period of 14 D[1]</td><td>-5FU: no modification
- Irinotecan 80 mg/m² (J1-J3)</td><td>- Gemcitabine 800 mg/m²
- Nab-Paclitaxel 100 mg/m²</td></tr>
<tr><td>Other[2]</td><td>No modification</td><td>No modification</td><td>- 5FU 1600 mg/m² (46h)
- Irinotecan 80 mg/m² (J1-J3)</td><td>- Gemcitabine 800 mg/m²
- Nab-Paclitaxel 100 mg/m²</td></tr>
</table>

1. In case of non-recovery of toxicities at D14: gastrointestinal (grade > 2 diarrhoea persistence) or haematological (persistence of grade> 2 for ANC or grade> 1 at D21 for platelets), we will carry out reductions in doses recommended for grade 3.
2. Except: alopecia, cholinergic syndrome and nausea/vomiting in the absence of adequate treatment
3. In case of persistent grade 3 neutropenia despite dosage adjustment and administration of G-CSF, Nab-Paclitaxel will be reduced to 75 mg/m².
If, despite these dose adaptations, at D14 there is a persistence of grade> 2 for ANC or grade> 1 for platelets, the patient will exit the study.
4. G-CSF: WBC growth factors

7.3 Dose adaptation related to the occurrence of febrile neutropenia

The treatment should be discontinued until resolution of fever and recovery of an ANC rate of $\geq$ 1500/mm^3. The treatment will be resumed according to the recommended dosage reductions for grade 3, on condition of administration of G-CSF.
If febrile neutropenia occurs during treatment with gemcitabine + Nab-Paclitaxel, while doses have already been reduced, Nab-Paclitaxel will be reduced to 75 mg/m².

7.4 Dose adaptation related to the onset of peripheral neuropathy

Dose adjustment will depend on the scale of peripheral neurological toxicities CTCAE v4 (Appendix 6).
Gemcitabine or FOLFIRI.3 will be continued with no dose modification.
In the event of grade 1 or 2 peripheral neuropathy, dose adjustment is not recommended.
In the event of $\geq$ grade 3 peripheral neuropathy, Nab-Paclitaxel must be suspended until recovery from $\leq$ grade 1 and then continued at 100 mg/m².
If grade 3 neuropathy occurs when Nab-Paclitaxel doses are already reduced, it should be suspended until recovery of grade $\leq$ 1 and then continued at 75 mg/m².

7.5 Dose adjustment in case of occurrence of pulmonary embolism

Clinically asymptomatic or mild pulmonary embolism can be treated with low molecular weight heparin without suspension of treatment.
In patients with moderate to severe pulmonary embolism (grade 3-4), treatment should be permanently discontinued and the patient should stop the protocol treatment.

Premedication, concomitant treatment and contraindicated treatment

The treatment considered necessary for patient well-being can be administered at the discretion of the investigator.
The subcutaneous administration of growth factor is permissible:
According to EORTC 2010 [38] recommendations, the risk of febrile neutropenia should be assessed before each chemotherapy cycle. The validated risk factors are: age> 65 years, a history of febrile neutropenia and advanced disease.

In the event of severe neutropenia, i.e. grade 3-4, patients are at high risk of febrile neutropenia and infection notably in the event of concomitant diarrhoea. If these symptoms occur, dosage adjustments are planned for the next treatment and the prescription of hematopoietic growth factors should be considered.

The administration of hematopoietic growth factors is not routinely recommended at the 1st NAB paclitaxel / GEMCITABINE or FOLFIRI.3 treatment, however they may be specified in each case depending on the patient's clinical condition. Treatment with lenograstim (GRANOCYTE®), filgrastim (Neupogen®, ZARZIO®) or pegfilgrastim (Neulasta®) is advisable.

The concomitant opioid treatment as well as pain assessment (VAS) should be reported in the case report. Data should be collected from the inclusions visit and throughout the treatment.
For pain assessment, the patient expresses their degree of pain on a scale of 0-10 (0 being "no pain" and 10 being "worst pain imaginable"

Contraindicated treatments

5FU: Yellow fever vaccine, live attenuated vaccines, and phenytoin for prophylactic purposes.

Irinotecan: association with St. John's wort, yellow fever vaccine.

Nab-paclitaxel: No interaction study has been performed, caution is required when using inhibitors or enzyme inducing drugs.

8. BIOLOGICAL STUDY LOGISTICS

For patients who have signed the biological informed consent form, details of the biological sub-study are located in Appendix 3 of this protocol.

Necessary samples
- A blood sample of 2 EDTA tubes of 5 (or 7) ml prior to starting treatment (during inclusion review or before the 1st treatment).

The tubes are sent, via DHL box provided at opening of the centre to:

Centre de Ressource Biologique EPIGENETEC
Unité UMR-S 1147
45 rue des Sts Pères, 75006 PARIS
Diriected by Pr Pierre LAURENT-PUIG

Only use the DHL box containing the **INSERM Unit U775 DHL paking slip.**

After sending this box, the box required for the inclusion of the next patient will be sent by EPIGENETEC.

- Paraffin embedded tumour block.

Dispatch blocks or slides via maxi letter provided to the centre at opening:

Centre de Ressource Biologique EPIGENETEC
Unité UMR-S 1147
45 rue des Sts Pères, 75006 PARIS
Directed by Pr Pierre LAURENT-PUIG

In case of logistics questions or problems, contact Claire MULOT at +33(0) 1 42 86 38 61, claire.mulot@parisdescartes.fr.

9. PATIENT MONITORING

9.1 Before each treatment administration

- Clinical exam: weight, WHO
- Evaluation of tolerance (toxicity according to NCI-CT v4.0) including systematic evaluation of the peripheral neuropathy according to the NCI-CT v4.0 scale (Appendix 6)
- Concomitant morphine treatment and pain assessment by VAS
- FBC, platelets, total bilirubin, free and conjugated, serum creatinine, sodium, potassium

If necessary provide for the administration of growth factors in subsequent treatment.

9.2 Quality of life questionnaire

QLQ-C30 version 3.0 every month during the first 4 months and then every 2 months

9.3 Assessment every 8 weeks

Patients will be evaluated every 8 weeks by:

- Clinical tests: weight, WHO, evaluation of the peripheral neuropathy according to the NCI-CT v4.0 scale and the mTNS simplified scale (Appendix 6)
- Evaluation of toxicities from the preceding cycle
- Concomitant morphine treatment and pain assessment by VAS

- Quality of Life Questionnaire QLQ-C30 Version 3.0 (every month during the first 4 months and then every 2 months)
- Biological tests: FBC, platelets, bilirubin (total and conjugated), PT, PAL, ASAT, ALAT, sodium, potassium, calcium, serum creatinine, creatinine clearance (MDRD), albuminemia, LDH.
- Pregnancy test for women of childbearing age
- Markers: CA 19-9, CEA
  Morphological Rating: CAP CT-scan or MRI if contraindication to injected CT scan
  A CAP CT-scan at 6 months after initiation of treatment is MANDATORY (whatever the number of treatments carried out, in order to assess the primary endpoint unless the patient is subject to prior progression)

9.4 Follow-up after stopping treatment

a/ **Within 30 days** for evaluating the toxicity of the last treatment:

- Biological tests: FBC, platelets, bilirubin (total and conjugated), PT, PAL, ASAT, ALAT, sodium, potassium, calcium, serum creatinine, MDRD creatinine clearance, albuminemia, LDH
- Evaluation of toxicities from the preceding cycle
  Pregnancy test

b/ **After radiological or clinical progression (as defined in 1.1),** patients will be monitored every 2 to 3 months up to death:

- Clinical exam: weight, WHO
- Evaluation of persistant toxicities
- Evaluation of the peripheral neuropathy 2 months after stopping the study treatment by mTNS simplified scale (Appendix 6)
  CAP-CT scan (or MRI)
- Quality of life questionnaire QLQ-C30 version 3.0

c/ **After premature discontinuation of treatment other than for progression*,** patients will be monitored in the same way every 8 weeks until progression:

- Clinical exam: weight, WHO
- Evaluation of persistant toxicities
- Evaluation of peripheral neuropathy 2 months after stopping the study treatment by mTNS simplified scale (Appendix 6)
- TAP-CT scan (or MRI)
- Quality of life questionnaire QLQ-C30 version 3.0
- Tumoral markers

* Toxicity, disease progression, withdrawal of consent, lost to follow-up, patient refusal, pregnancy or suspected pregnancy

10. SUBSEQUENT TREATEMENT

Recommended treatment in the event of progression or toxicity

- In sequential arm A (alternating nab-paclitaxel/gemcitabine and FOLFIRI.3):

If the patient must prematurely stop one of the two treatments due to limiting toxicity or progression in a sequence (for example nab-paclitaxel/gemcitabine), the investigator must absolutely pursue the other sequence (in this case FOLFIRI. 3) until progression.

In case of further progression, the investigator will assess the use of further treatment.

- In the reference arm B (nab-paclitaxel/gemcitabine),

In case of premature discontinuation of treatment, the investigator will assess the use of further treatment.

11. MANAGEMENT OF SERIOUS ADVERSE EVENTS (SAE)

Safety endpoints

The safety assessment will be carried out by assessing the general and clinical condition of patients and by the collection of events occurring between visits during consultations, by regular blood tests. The toxicities shall be evaluated by the NCI-CTCAE toxicity scale version 4.0 (Appendix 6).
In an emergency, the patient, family members or physician should call the investigator to inform them of an event.

Definitions

a. Adverse event (AE)
An adverse event is a harmful event occurring in a person volunteering for biomedical research, whether this event is related or not to the research or product of this research.

All adverse events will be recorded in the case report form in the pages provided for this purpose.

b. Serious Adverse Event (SAE)
Considered a serious adverse event, is any event
- causing death,
- life threatening,
- causing hospitalisation or extension of hospitalisation,
- causing permanent disability or serious temporary incapacity
- causing a congenital abnormality, foetal malformation or abortion,
- medically significant (e.g.: overdosage, secondary cancer and new issue that may be considered medically significant)

The terms disability and incapacity correspond to any temporary or permanent physical or psychological disability, clinically significant and devastating to physical activity and/or the quality of life of the patient.

Considered medically significant are all clinical events or laboratory results assessed as serious by the investigator and not corresponding to the above-defined severity criteria. They may pose a risk to the patient and require medical intervention to prevent an outcome corresponding to one of the severity criteria mentioned above e.g.: overdosage, secondary cancer, pregnancy and new issue that may be considered medically significant).

Pregnancy is an exclusion criterion in this trial. However, if a pregnancy is discovered after inclusion, the patient should be excluded from the trial. The sponsor should be informed immediately via the serious adverse event report card (no severity criterion shall be checked). The patient should be monitored until the end of pregnancy and the outcome whatsoever, must be reported to the sponsor. This declaration and follow-up shall also apply in the context of a pregnancy in a patient's partner.

If the pregnancy outcome falls within the scope of the definition of serious adverse events (spontaneous or therapeutic abortion requiring hospitalisation, foetal death, congenital anomaly...) the investigator must follow the SAE reporting procedure.

All neonatal deaths occurring within 28 days following the birth should be reported, regardless of the causality as an SAE. In addition, any infant deaths occurring after these 28 days and suspected by the investigator to be related to in utero exposure to drug testing must also be reported to the sponsor within 24 hours of the Investigator becoming aware of the event by following the procedure for reporting SAEs.

c. Adverse Event
Any harmful and unintended response to an experimental drug whatever administered dose or any experimental element. The AE is severe if it presents a serious criterion.

d. Suspected Unexpected Serious Adverse Reaction (SUSAR)
A Suspected Unexpected Serious Adverse Reaction is an event not consistent or different by its nature, intensity or evolution in relation to the product reference document (or pCRs).

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

f. Intensity (or severity)
The intensity criteria should not be confounded with the severity criteria that are used to define the declaration procedure.
The event intensity is graded according to the CTCAE version 4.0 classification (Appendix 4). The intensity of adverse events not listed in this classification shall be evaluated according to the following scale:
- Mild (grade 1): not affecting the patient's usual activity.
- Moderate (grade 2): disrupts the patient's usual activity.
- Severe (grade 3): prevents the patient's usual activity.
- Very severe (grade 4): Life-threatening consequences/urgent intervention indicated.
- Death (grade 5)

g. Causality
- Related: an event is related when there is suspected reasonable possibility of causality between the product undergoing study and the event
- Non-related: an event is said to be non-related when a causality between the event and the trial product cannot reasonably be suspected
- Unlikely: causality is "questionable" when there is doubt as to the causality between the event and the product under study (then the relationship can neither be formally excluded nor formally affirmed)

h. Sponsor's responsibility
On receiving the serious adverse event declaration determined by the investigator, the sponsor must advise on the causal link between the serious adverse event and the products undergoing study.
If the serious adverse event is connected by the investigator and/or sponsor to the product being studied (it is therefore a serious adverse event), they must demonstrate the expected or unexpected character of this effect.
If it is an unexpected serious adverse event, or a new event, the sponsor drafts an initial report to be transmitted to the ANSM, the EC and the EMA (via EudraVigilance) within 7 days in case of death or if life-threatening otherwise within 15 days.

Events not considered serious

The progression of the disease should not be treated as an SAE.

Events potentially related to the progression but that can also be secondary to the treatment shall continue to be reported (e.g. thromboembolic events, haemorrhagic phenomena, perforations…)

Due to the severity of the disease in this study, certain conditions defined as SAEs shall be excluded from the SAE declaration procedure, i.e.:

Hospitalisation or surgery related to treatment of the disease. However, hospitalisation or extension of hospitalisation for a complication of these treatments should be reported as an SAE.

Hospitalisation in order to simplify study treatment or procedures.

In this trial reference documents will be:
- For nab-paclitaxel, Abraxane® summary of product characteristics (Appendix 7)
- For gemcitabine, Gemzar® summary of product characteristics (Appendix 7)
- For 5-fluorouracile, Fluorouracile Ebewe® 50 mg summary of product characteristics (Appendix 7)
- For folinic acid, Elvorine® summary of product characteristics (Appendix 7)
- For irinotecan, Campto® summary of product characteristics (Appendix 7)

Mcm versions used for the expected or unexpected character definition will be those in effect at the time of the analysis.

Course of action

The investigator informs the sponsor of all (Expected and unexpected) Serious Adverse Events whether or not caused by the research and occurring during the study or during the 30 days after the last treatment dose.

All delayed Serious Adverse Events (occurring after this 30-day period) considered reasonably related to (x) protocol or research treatment must be declared without limitation of delay.

The declaration is carried out by faxing the "notification of a serious adverse event" form (Appendix 9) documented as precisely as possible, dated and signed, within 24 business hours after initial observation to the **Centre for Randomisation Management Analysis (CRGA) of the FFCD: by fax to 03 80 38 18 41.**

The investigator is responsible for the appropriate medical follow-up of patients until recovery, stabilisation of the event and/or the death of the patient. This can sometimes imply that this monitoring is extended after the patients exit from the trial.

They transmit the additional information to the sponsor with an SAE report form (by ticking the "Follow-up" box and incrementing the number, to specify that it is a follow-up report and not an initial report) within 24 hours after its receipt. They will also send the last follow-up at resolution or stabilisation of the SAE.
They shall respond to requests for additional information in order to document the initial observation.

12. STATISTICAL ANALYSIS

12.1 Provisional study timetable

Rhythm of start of inclusions: 5 patients per month
Start of inclusions: April 2015
End of inclusions: 24 months after the beginning of inclusions i.e. April 2017
First analysis: October 2017

12.2 Endpoints

12.2.1 Primary efficacy endpoint

The primary endpoint is the rate of patients alive without progression 6 months after inclusion.
The progression is clinically and/or radiologically assessed by the investigator (as defined in 1.1) according to RECIST v1.1 criteria.

12.2.2 Secondary endpoints

The secondary endpoints are:

- Overall survival (OS): defined as the time interval between the randomisation date and the date of death (all causes). The patients alive will be censored at the end-point or the date of the latest event
- The objective response rate (ORR): defined as complete or partial response rates in imaging by RECIST v1.1 over the entire treatment
- The best response to treatment shall be evaluated from imaging throughout the treatment
- Progression-free survival: defined as the time interval between the randomisation date and the date of first progression (clinical and/or radiological) or death (whatever the cause). Living patients without progression will be censored at the end-point or date of latest event.
- Time to discontinuation of treatment: defined as the time interval between the randomisation date and treatment stop date (regardless of cause) or date of latest events for living patients without stopping treatment.
- Toxicities are evaluated according to NCI CTC v4.0.
- Peripheral neuropathy toxicities are evaluated according to the Mtns simplified scale (Modified Total Neuropathy Score of GOG-Taxane scores)
- The time to first occurrence of grade 3 and 4 toxicity: defined as the time interval between the date of randomisation and the first occurrence of a 3.4 grade event.
- Quality of life (assessed according to the EORTC QLQ-C30 questionnaire): This scale comprises 30 items with 15 dimensions for calculating 15 scores (5 functional ability scores, 8 symptom scores, an overall score, and a financial problems score). These scores will be calculated and described at inclusion. Of an exploratory manner, time to deterioration of the overall health score will be calculated: it is defined as the time interval between the date of randomisation and the date of reduction of over 5 points compared to the baseline (5 points being considered the minimum to define a clinically significant difference) or death.

12.3 Calculation of the number of required subjects, statistical hypotheses

The hypotheses for calculating the number of subjects required are:
H_0: rate of patients alive without progression of 40 % at 6 months is insufficient.
H_1: rate of patients alive without progression of over 40 % at 6 months is hoped for.
A rate of 60 % is expected

By using the exact binomial method, an alpha one-sided 5% risk error and a power of 90%, it is necessary to include 56 patients per arm. The decision rules apply to the experimental arm only.

At the end of recruitment, during the analysis:
- If 27 patients or less are living without progression the treatment is judged ineffective.
- If 28 patients or more are living without progression we then reject H_0 and the treatment will be considered of interest.

By considering a rate of patients lost to follow-up or not evaluable by 10%, it is necessary to include 62 patients per arm or **124 patients in all.**

Analysis of the primary endpoint shall be carried out in modified intent to treat in all **evaluable** patients included in the study regardless of the eligibility criteria and the treatment received.

Patients with no evaluation at 6 months will be reviewed using the following rules:
- If the patient has a later evaluation (7 months or more) and is not in progression at that date they shall be considered as progression-free at 6 months
- If the patient has documented progression of more than 6 months without imagery at 6 months then the patient shall be considered in progression at 6 months.

If a progression is documented before the 6-month evaluation, the patient is considered as in progression at 6 months.

12.4 Statistical analysis plan

Population analysis:
Patient description will be conducted with *intention to treat* (ITT) on all randomised patients regardless of their eligibility criteria and treatment received.

Analysis of the primary endpoint will be conducted with *modified intent to treat* (mITT) among all randomised patients evaluable (clinically and/or radiologically) regardless of their eligibility and the treatment received.

The *tolerance* population is defined as all randomised patients who have received at least one dose of chemotherapy (regardless of the product).

Descriptive analyses
The continuous variables will be described using mean, standard deviation, median, minimum, maximum, and the inter-quartile range (Q1-Q3).

Qualitative variables shall be described using frequencies and percentages. The percentages will be calculated without taking into account the missing data modality.

Censored data will be estimated and plotted using the Kaplan-Meier method. The median times and rates at different temporalities shall be described as well as their confidence intervals at 95%.
Median follow-up will be determined by the reverse Kaplan-Meier method.

Tolerance analysis

The number of treatments, the dose received and the percentages of actual dose received on theoretical dose will be described, as well as the percentage of patients with at least one dose modification or at least an administrative report.
The toxicities will be described by treatment arm, the number of patients and toxicities according to various grades and SOC. They will also be described by grouping grades 1-2 versus 3-4-5.
Every six months a safety report will be provided by pharmacovigilance centres to all the study investigative centres.

13. STUDY COMMITTEES

13.1 Independent committee

An Independent Committee will be set up and will include at least two gastro-oncologists, a statistician/methodologist and a pharmacovigilance expert. The independent committee will be referred to at any point during the protocol when the sponsor deems it necessary.

13.2 Steering committee

A Steering Committee will be set up. The steering committee director shall be the study coordinator. This committee will also include the co-coordinators, the FFCD project manager, the FFCD statistician and the President of the Biological Research Committee. Its mission among others will be to make decisions related to research management (amendment, premature termination if required…). This committee shall meet whenever necessary throughout the study. The steering committee will make the necessary decisions concerning substantial amendments to the protocol, the closing or extension of the study.

13.3 Medical review

A medical review board shall be set up in order to improve the quality of clinical data collected. In case of discrepancy between the data provided by the investigator and those in the medical review, requests for clarification will be sent to the investigator by data management.

13.4 Biological Research Committee

A Biological Research Committee will be established; it will manage the problems related to sampling, their addition to the biobank and the organisation of their analysis. The committee will meet regularly and report its proposals to the Steering Committee. This committee will include among others the study coordinator and a biologist; it will be chaired by Pr Pierre LAURENT PUIG.

14. BASIC INFORMATION AND STUDY JUSTIFICATION

14.1 Pancreatic cancer, a prognosis with a modest improvement

Due to its very poor prognosis, which puts it in fifth position in cancer deaths, but also due to its steadily increasing incidence in Western countries (1), pancreatic adenocarcinoma is a major challenge for therapeutic strategies in gastrointestinal oncology. Due to the aggressiveness of this cancer, and its initially insidious mode of development, around 85% of patients develop unresectable disease at diagnosis. In the presence of visceral metastases, median survival of untreated patients does not exceed three to six months, and among patients who could benefit from curative resection, more than 80% relapse within 2 years after surgery (2).
The chemo/radiation resistance of this cancer, when the patient's general condition authorises systemic treatment, explains the multitude of negative clinical trials (3) and the maintenance for years of Gemcitabine as the reference treatment in first line metastatic treatment (4).
Nevertheless, in recent years, 2 positive Phase III trials have given hope to caregivers and patients:

- the PRODIGE 4/ACCORD 11 (5) study assessing the multiple drug chemotherapy regimen FOLFIRINOX, with 5-fluorouracil, oxaliplatin, irinotecan and folinic acid
- and the MPACT study (6), evaluating the combination of Gemcitabine with Nab-Paclitaxel: a nanoparticle albumin molecule enabling the vectorisation of Paclitaxel in tumour cells and the optimisation of its pharmacokinetics.

14.2 The development of multi-drug chemotherapy

The anti tumour effect of irinotecan in cellular cultures of pancreatic adenocarcinoma appears promising, with an inhibition of tumour growth greater than cisplatin, mitomycin-C and fluorouracil (7). However, the observed response and survival rate remains disappointing (8-11). Diagrams for enhancing this anti-tumour effect have been developed by combining irinotecan to 5-FU in patients with colorectal cancer (12,13). Among these, FOLFIRI.3 wherein irinotecan is administered before and after a 46-hour continuous infusion of 5-FU, has yielded encouraging results (14). We have tested this regimen in a phase II trial in patients with metastatic pancreatic cancer, with an objective response of 37.5%, a median OS of 12 months for an acceptable tolerance (15).

14.3 The FIRGEM study, the first sequential strategy in metastatic pancreatic cancer

Given these results, we have proposed a scheme combining FOLFIRI.3 and Gemcitabine alone, sequentially, with the aim to increase the survival of patients while preserving quality of life. This innovative approach was underpinned by the results of certain studies, indicating that the administration of different models of sequential multidrug regimens was independently associated with overall survival in patients with pancreatic adenocarcinoma and metastatic colorectal cancer (16,17). Accordingly, it has been proven that sequential strategies using chemotherapy without cross-resistance can increase the anti-tumour effects of these drugs, and limit their cumulative and non-cumulative toxicities.
We conducted a randomised multicenter phase II trial: the FIRGEM trial comparing an experimental sequential arm consisting of FOLFIRI.3 alternating with Gemcitabine, to the reference arm: Gemcitabine as monotherapy in patients with non-pretreated metastatic pancreatic adenocarcinoma (Trouilloud et al, ASCO 2012). This study has helped to establish the FIRGEM strategy as an effective first-line treatment option in patients with metastatic pancreatic cancer who are in good general condition. The main criterion has been reached, with a progression-free survival rate at 6 months of 45% in the FIRGEM arm, against only 26% in the gemcitabine arm. This encouraging progression-free survival rate was also maintained at 12 and 18 months (26.2% and 18% respectively), when the median PFS was 5 months. In addition, an impressive objective response rate (40%) was observed in the FIRGEM arm compared to gemcitabine alone (11%). These results confirm the initial phase II trial evaluating the FOLFIRI.3 regimen (objective response rate of 37.5%) (15) in patients with pancreatic cancer, and compares favourably to the rates in recent phase III trials (31.6% and 23% in trials evaluating FOLFIRINOX and Gemcitabine + Neb - Paclitaxel respectively).
Regarding the median overall survival, it was 11 months with FIRGEM, against 8.2 months with gemcitabine alone (HR: 0.710; 95% CI: 0.457 to 1.103). Once again, the sequential experimental design has given promising results, in the range of those observed with FOLFIRINOX (11.1 months). The tolerance profile of the FIRGEM strategy was acceptable, with a higher hematologic toxicity in the Gemcitabine arm alone. It is worth noting that a limiting sensory neuropathy with the sequential design was not observed, and a significant increase in time to deterioration of quality of life was objectified compared to the gemcitabine as monotherapy arm.

14.4 FIRGEMAX, the optimisation of 4 alternating chemotherapies.

Whereas Nab-Paclitaxel significantly improves the survival of patients with metastatic pancreatic cancer when combined with Gemcitabine, associating this drug with the FIRGEM strategy could prove particularly interesting. Adding this new option would enable anti-tumour action based on four different drugs without any cross-resistance described between them, administered in succession in the first four months of treatment. This new concept, consisting of three therapies of Gemcitabine + Nab-paclitaxel, followed by two additional non-neurotoxic chemotherapy treatments of FOLFIRI.3, would give the patient more than 29 days necessary to recover a potential secondary neurotoxicity with Nab-Paclitaxel. This "rest period" without Nab-Paclitaxel could help eliminate or at least significantly delay the onset of cumulative sensory neuropathy induced by this molecule. Consequently, the sequential administration of the two proposed chemotherapy regimens would act as a "stop and go" strategy.

We therefore propose to start the FIRGEMAX phase II randomised trial, assessing the reference arm Gemcitabine + Nab-Paclitaxel and a sequential arm with two months of Gemcitabine + Nab-paclitaxel, followed by two months of FOLFIRI 3 before continuing this alternating sequence.

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16. ADMINISTRATIVE CONSIDERATIONS

STUDY SPONSOR

The study sponsor is the French Federation of Digestive Oncology (FFCD). The study was registered under the number EudraCT 2014-004449-28.

REMINDER OF TEXTS IN FORCE

This trial will be conducted according to the French law in force in accordance with the ethical principles of the Declaration of Helsinki 1964 and its revisions, the International Conference on Harmonization (ICH) on Good Clinical Practice (GCP) guidelines (ICH-E6, 7/17/96), with EU directives (2001/20/EC) on the conduct of clinical trials, the modified (12.20.98) French law for the Protection of persons involved in biomedical research known as "Loi Huriet" and the provisions of the "Information technology and Freedom of the Individual" (law n°78-17 dated 6/01/78 modified by law n° 94-548 dated 1/07/94.

CIVIL LIABILITY INSURANCE

Insurance has been obtained by the sponsor on 10/11/2014 under the number 137.68, in accordance with article L 1121-10 of the code of public health (Appendix 9).

REQUEST FOR AUTOHRISATION FROM THE ETHICS COMMITTEE AND THE ANSM

This protocol has received approval from the Ethics Committee IDF VIII on 2/12/2014 (Appendix 12).
This protocol has received the approval of the ANSM (French National Agency for Medecines and Health Products safety on 22.05.2015 (Appendix 13).

COLLECTION OF INFORMED PATIENT CONSENT

After informing the patient the investigator agrees to collect their written clinical and biological consent (information and consent forms in Appendix 1) prior to registering the patient in the study. The investigator shall retain a copy of this consent for 15 years, to be submitted to the regulatory authorities for inspection. The original must be given to the patient.

In accordance with the Cancer plan recommendations (Measure 4.3.). This document has been submitted to the Committee of Patients for Clinical Research (CRPC) of the National Cancer League

HOSPITAL ADMINISTRATION INFORMATION AND RESEARCH AGREEMENT

Prior to starting this study, the hospital administrators will be informed by the sponsor of the investigators interest in participating in this trial.
A research agreement will be established between the administrator of the investigating centre and the sponsor.

DATA STORAGE

The files shall remain confidential and may only be consulted under the responsibility of the physicians charged with the care of the patients. The sponsor and health authorities in the event of an inspection will have direct access to these documents.
At the end of the trial, the case report forms will be kept for 15 years by the investigator.

IT SUPPORT

According to the text of Law n° 78-17 of January 6, 1978 amended by the Law of August 9, 2004 relating to computers, files and liberties, trial data will be stored in a databank of the Centre for Randomisation, Management and Analysis of the FFCD, with the exclusion of elements relating to the identity of the patients.

DATA TREATMENT

The Centre for Randomisation, Management and Analysis (CRGA) of the FFCD shall be responsible for the management and analysis of the data.

MONITORING, QUALITY ASSURANCE AND INSPECTION BY THE AUTHORITIES

The investigator agrees in advance that the included patient records be consulted by a person authorised by the Sponsor and/or the health authorities to carry out an audit. The programmed on-site visits to consult files with investigator agreement may take place during or after the period of inclusion in the trial.
The FFCD mobile CRA will monitor this trial.

17. RULES FOR PUBLICATION

They shall comply with those established by the PRODIGE Group (Appendix 10).