PROTOCOL PAMELA 70

A) IDENTIFICATION OF THE CLINICAL TRIAL	
SPONSOR NUMBER:	ICO-N-2014-01
N° EUDRACT:	2014-000539-17
VERSION AND DATE:	V5 OF 12/06/2018
TITLE: ***Phase-2 study evaluating Overall Response Rate (efficacy) and Autonomy Daily living preservation (tolerance) of "FOLFIRINOX " pharmacogenetic dose adjusted, in elderly patients (70 yo. or older) with a metastatic pancreatic adenocarcinoma.***	
SHORT TITLE: **PAMELA 70**	
COORDONNATOR:	Docteur Sandrine HIRET – service d'Oncologie Médicale ICO René Gaudducheau, Bd Jacques Monod 44805 SAINT HERBLAIN
ESTIMATED NUMBER OF CENTRES: 6	**NUMBER OF PATIENTS**: 72

B) IDENTIFICATION OF SPONSOR	
SPONSOR: ICO, DRCI-Cellule de Promotion	
PROJECT MANAGER:	**MME VALERIE PACTEAU** **Tel : 02 40 67 99 00 - 9168**

C) GENERAL INFORMATION
INDICATION: Metastatic pancreatic carcinomas.
DESIGN: Phase II study, opened, multicentric
MAIN OBJECTIVE: The main objective is the simultaneous evaluation of the objective rate of answer and toxicity of her(it) of the protocol FOLFIRINOX administered to doses adapted at patients of 70 and more years old.
SECONDARY OBJECTIVE • Efficiency evaluation • Tolerance evaluation • Quality of Life (QoL) and clinical profit

INCLUSION CRITERIA :

1. Histologically proven ductal pancreatic carcinoma
2. Metastatic disease
3. First-line treatment: No previous chemotherapy in metastatic stage but adjuvant treatment before relapse (secondary metastatic) is permitted, provide it has been administered more than 6 months before)
4. Age of 70 year or above
5. Normal DPD enzyme level or partial defect (excluding total defect)
6. Adequate bone marrow reserve: as indicated by: neutrophils >1500/mm3, platelets >100,000/ mm3, Hb >10.0g/dL.
7. Adequate Renal function as indicated by: MDRD creatinine clearance > 50ml/min.
8. Adequate hepatic function as indicated by: serum bilirubin < 1.5 times the upper limit of normal, AST and ALT < 2.5 times the upper limit of normal, or < 5 times the upper limit of normal if liver metastases are present.
9. Written informed consent must be obtained prior to protocol-specific procedures are being performed

EXCLUSION CRITERIA :

1. Other than ductal pancreatic carcinoma: namely endocrin tumors, acinar cells carcinoma, cystadenocarcinoma or adenocarcinoma of the ampulla of vater
2. Non-metastatic but locally advanced pancreatic adenocarcinoma
3. Complete DPD deficiency
4. History of Cardiac failure or symptomatic coronary artery disease
5. Autonomy Daily Living score by Katz <4
6. Prior treatment with FOLFIRINOX (adjuvant)
7. Major comorbidity likely to be an obstacle to treatment
8. Active or uncontrolled infection such as HIV or chronic B or C hepatitis
9. Uncontrolled diabetes mellitus
10. Prior peripheral neuropathy, grade > 2
11. Inflammatory bowel disease localized on the colon or rectum; bowel obstruction or severe uncontrolled diarrhea
12. Previous or concomitant malignancies other than effectively treated carcinoma in situ of the cervix or non-melanoma skin cancer
13. Hereditary fructose intolerance
14. Persons deprived of liberty or under guardianship
15. Any social, geographical or psychological condition which would compromise the ability to fully comply with the trial procedures and treatments

PRIMARY ENDPOINT:

Response rates in the phase III study comparing Folfirinox versus gemcitabine were 31.6% versus 9.4%, respectively. We therefore set a minimum threshold of acceptable efficacy at 10%, for an expected radiological response rate of approximately 25%.

Toxicity will be assessed through loss of autonomy impacting Katz's Activities of Daily Living (ADL). Since patients' baseline ADL score (rated from 0 to 6) must be at least 4/6 at inclusion, any decrease strictly greater than 1 (i.e., 1.5 points or more) is considered indicative of a significant loss of autonomy and will be deemed unacceptable if 50% or more of treated patients are affected. We expect that 30% or fewer of the included patients will experience a loss of autonomy of 1.5 points or more due to the treatment.

SECONDARY ENDPOINTS:

• Efficacy assessment
Assessment of progression-free survival and overall survival.

• Safety assessment
Treatment tolerability will be graded using the NCI-CTC 4.0 scale and will also be evaluated using the ADL scale.
The following will be analyzed:

- the incidence of grade 3–4 hematologic toxicities (particularly neutropenia and febrile neutropenia),
- the incidence of gastrointestinal toxicities (notably diarrhea and mucositis),
- the incidence of peripheral neuropathies.

• Quality of Life (QoL) assessment
Patients' quality of life will be evaluated using the EORTC QLQ-C30 v3.0 questionnaire at baseline, during each chemotherapy cycle, and at the end of treatment.
A Comprehensive Geriatric Assessment (CGA) will also be proposed, including:

- the IADL score (Instrumental Activities of Daily Living, Lawton scale),
- comorbidity assessment (CIRS-G),
- nutritional assessment (MNA),
- the "Get Up and Go" test evaluating sitting-to-standing transfers, walking, and directional changes,
- the Mini-Mental State Examination (MMSE) evaluating cognitive function.

D) DESCRIPTION OF THE INVESTIGATIONAL MEDICINAL PRODUCTS

DRUGS: **FOLFIRINOX regimen**:

Name of the drug (INN)	Route of administration	Dosage per administration
OXALIPLATINE	IV infusion	85 mg/m2
Name of the drug (INN)	Route of administration	Dosage per administration
FOLINIC ACID	IV infusion	400 mg/m2
Name of the drug (INN)	Route of administration	Dosage per administration
IRINOTECAN	IV infusion	de 130 à 180 mg/m2
Name of the drug (INN)	Route of administration	Dosage per administration
5 FLUORO-URACILE	IV infusion	de 1600 à 2000 mg/m2

THERAPEUTIC REGIMEN

- ***Oxaliplatine***

Dosage: **85 mg / m²**
Route: 2-hour IV infusion
Date of administration: D1 of each cycle.

- ***Folinic acid***

Dosage: **400 mg / m²**
Route: 2-hour IV infusion, **after infusion of oxaliplatine**
Date of administration: D1 of each cycle.

- ***Irinotecan***

Dosage: **Determined according to the UGT1A1 genetic status:**

- In 6/6 or 6/7 homozygous patients:

Start the 1st cycle at 150 mg/m², then increase from the 2nd cycle onward, depending on clinical and laboratory tolerance, in 10% increments, up to a maximum of 180 mg/m².

- In 7/7 homozygous patients:

Start the 1st cycle at 130 mg/m², then increase from the 2nd cycle onward, depending on clinical and laboratory tolerance, in 10% increments, up to a maximum of 150 mg/m²

Route: 90-min IV infusion, **within 30 min after oxaliplatine infusion**
Date of administration: J1 de chaque cycle.

- ***5-FU***

Dosage: According to DPD pharmacogenetics determined at baseline:

- • If no DPD deficiency:

Start at 1600 mg/m² (instead of 2400 mg/m² in the standard Folfirinox regimen), then increase at each cycle, depending on clinical and laboratory tolerance, to 1800 mg/m² at the 2nd cycle, then 2000 mg/m² from the 3rd cycle onward.

- • In case of partial DPD deficiency:

Start at 1200 mg/m² (instead of 2400 mg/m² in the standard Folfirinox regimen), then increase at each cycle, depending on clinical and laboratory tolerance, to 1800 mg/m² at the 2nd cycle, then 2000 mg/m² from the 3rd cycle onward.

Route: continue IV infusion of 46 hours, **after the end of acide folinique infusion**.

Date of administration: D1 to D3 of each cycle

DURATION OF TREATMENT: 24 weeks: 12 cycles Q2W

E) STATISTICAL ANALYSIS

NUMBER OF REQUIRED SUBJECTS AND STATISTICAL ANALYSIS

A two-stage analysis is planned, according to the Bryant and Day method [30], with a β risk of 5% of wrongly rejecting a treatment that is effective and has acceptable toxicity, and an α risk of 10% of wrongly accepting a treatment that is insufficiently effective or too toxic.
If we choose:

- Unacceptable Response Probability (Pr resp0) = 10%
- Acceptable Response Probability (Pr resp1) = 25%
- Unacceptable Toxicity Probability (Pr tox0) = 50%
- Acceptable Toxicity Probability (Pr tox1) = 30%

Then:

1st stage:
If, 12 weeks after the inclusion of the 34th patient, the following is observed:

- Either ≥ 17 patients show a decrease of 1.5 ADL points or more: **the treatment is considered too toxic**.
- Or ≤ 3 patients show a tumor response: **the treatment is considered insufficiently effective.**

⇨ **In either case, the trial will be stopped at this first stage.**

2nd stage:
Otherwise, an additional 38 patients will be enrolled, for a total expected sample size of 72 patients.
Final evaluation criterion:
The investigational treatment will be considered a failure if:

- For toxicity: ≥ 31 patients experience a loss of autonomy of 1.5 ADL points or more, and/or
- For lack of efficacy: ≤ 10 patients achieve a tumor response.

The study will be considered a success if:

- at least 11 tumor responses are observed, and
- no more than 30 out of 72 evaluable patients experience a loss of autonomy (decrease in their ADL score).

Additional evaluation rules:

- All patients who receive at least one injection will be eligible for toxicity assessment.
- Efficacy assessment will be performed after at least 3 cycles, unless early discontinuation occurs, in which case the CT scan assessment will be advanced.
- All toxicities will be graded according to NCI CTC v4.0 criteria.
- Tumor response evaluation (CR, PR, and SD) will be performed according to RECIST v1.1 criteria.

SELECTION OF SUBJECTS INCLUDED IN THE ANALYSES

Statistical analyses will be performed on an intention-to-treat (ITT) basis, meaning that all enrolled subjects (including those incorrectly included or those who will not comply with the protocol) will be considered in the analysis. No exclusion will be allowed.

The analysis populations are defined as follows:

ITT population

- All enrolled patients.
- Any patient incorrectly included and/or without available primary endpoint data will be classified by default as a non-responder and as experiencing toxicity.

Modified ITT (mITT) population

- The eligible and evaluable subset of the ITT population:
- This excludes patients with major violations of inclusion/non-inclusion criteria and/or those without available endpoint data (death, early discontinuation, loss to follow-up, refusal of the CT scan, etc.).

F) BIOLOGICAL MATERIALS COLLECTED FOR THE RBM

Type of sample(s): blood plasma
Quantity collected: 1 tube of 8 mL

Plasma will be collected **before the infusion at Cycle 1 and Cycle 3**, and **at each radiological assessment** during treatment and follow-up **until disease progression**.

G) EXPECTED DURATION OF THE STUDY

INCLUSION PERIOD:
Enrollment will take place over a total of 66 cumulative months, taking into account a minimum 3-month suspension of recruitment after the inclusion of the 34th patient (Stage 1), in order to evaluate toxicity and tolerability in this initial cohort.

TREATMENT PERIOD: 12 cycles of FOLFIRINOX, (24 weeks)

FOLLOW UP PERIOD: Patients will be followed every 3 months at most, until disease progression or death, for a maximum duration of 3 years.