PRODIGE 37 - FIRGEMAX (FFCD 1406)

Phase II randomized multicenter trial evaluating sequential treatment with nab-Paclitaxel + Gemcitabine / FOLFIRI.3 versus nab-Paclitaxel + Gemcitabine as 1st line treatment in metastatic pancreatic cancer

Statistical Analysis Plan

Final analysis

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2 Abbreviations and definitions

SEE	Serious adverse event
HR	Hazard ratio
CI	Confidence Interval
ITT	Intention to treat
ITTm	Modified intention to treat
mTNS	modified Total Neuropathy Score
NCI-CTC	National Cancer Institute Common Toxicity Criteria
WHO	World Health Organization
PP	Per-protocol
RECIST	Response evaluation criteria in solid tumors
SG	Overall survival
PFS	Progression-free survival
SP	Tolerance population

3 Introduction

3.1 Objectives of the trial

3.1.1 Objective main

The primary objective of the study is to evaluate, in each arm, the rate of patients alive and free of radiological and/or clinical progression at 6 months.

3.1.2 Secondary objectives

The secondary objectives of the study are to evaluate:

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

3.1.3 Ancillary analyses

A biological ancillary analysis is planned to evaluate :

- Constitutional genetic polymorphisms that can influence the efficacy and tolerability of chemotherapy molecules (UGT1A1, ERCC1, MTHFR, DPD, TS ...)
- Immunohistochemical biomarkers predictive of treatment response thanks to a kerosene section study

4 Experimental design

4.1 Study diagram

This is a multicenter, randomized, non-comparative Phase II trial.

4.2 Treatment arms

In this study there are 2 treatment arms:

- **Arm A (experimental arm): Alternating 2 months of nab-Paclitaxel + gemcitabine with 2 months of FOLFIRI.3**

  Nab-Paclitaxel + gemcitabine (3 weeks/4 for 2 months) at D1, D8, D15 and at D29, D36, D43

  Then FOLFIRI.3 (a cure every 14 days for 2 months) at D1, D15, D29 and D43.
- **Arm B (reference arm): nab-Paclitaxel + gemcitabine**

  Nab-Paclitaxel + gemcitabine (3 weeks/4) at D1, D8, D15 and at D29, D36, D43

Treatment is continued until progression or unacceptable toxicity.

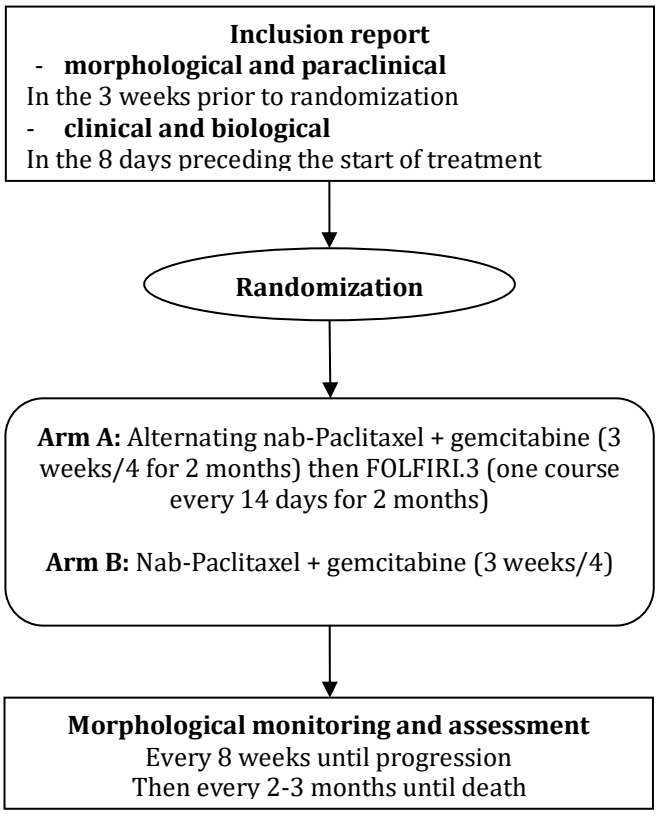
4.3 Randomization and blinding

The trial is open-label. Randomization is centralized and balanced between arms in a 1:1 ratio. The minimization technique will be used for treatment allocation by randomization stratifying on :

- the center
- WHO: 0 vs 1 vs 2
- Number of metastatic sites: 1 vs > 1

4.4 Chronological sequence

Each patient will follow the chronological sequence described below:



4.5 Justification of the number of subjects required

The assumptions used to calculate the number of subjects required were :

H0: A progression-free survival rate of 40% at 6 months is insufficient.

H1: A progression-free survival rate of over 40% at 6 months is hoped for.

A rate of 60% is expected

Using the exact binomial method, a 5% risk of one-sided alpha error and 90% power, it was necessary to include 56 patients per arm.

Assuming a 10% rate of patients lost to follow-up or unable to be assessed, it was necessary to include 62 patients per arm, for a **total of 124 patients**.

4.6 Test steps

4.6.1 Analysis Final

The final analysis will be performed once the information on the last patient included has been retrieved. The cut-off date for the analysis is the randomization date of the 124ème patient + 6 months.

At the end of recruitment, during analysis :

- If 28 or fewer patients are alive without progression at 6 months, the treatment is deemed ineffective.
- If 29 or more patients are alive without progression at 6 months, we reject H0 and conclude that the treatment is effective.

These decision rules apply only to the experimental arm, and will be recalculated if necessary, based on the number of patients actually evaluable.

4.6.2 Adjustments

Adjustments may be made to this analysis plan in the event of amendments to the protocol, or if phenomena not initially foreseen require statistical adaptations. In all cases, these modifications must be made before the database is frozen.

5 Study population for analysis

The study focuses on patients with metastatic pancreatic adenocarcinoma.

5.1 Definition of analysis populations

5.1.1 Intention-to-treat (ITT) population

The intention-to-treat population is defined as all patients randomized to the study, irrespective of eligibility criteria and treatment received. Patients will be analyzed in the treatment group allocated at randomization.

Analyses on this population will be carried out on an exploratory basis to confirm the results of the main ITTm analysis.

5.1.2 Population modified intention-to-treat (mITT)

The modified intention-to-treat population is defined as the ITT population of evaluable patients. A patient is considered evaluable if he or she has received at least one dose of treatment. Patients will be analyzed in the treatment group allocated at randomization.

A list of patients excluded from the ITTm population will be provided, together with the reasons for their exclusion.

All analyses will be carried out in ITTm, unless otherwise specified for certain criteria).

5.1.1 Per-protocol population (PP)

The per-protocol population is defined as all patients who met all the major inclusion criteria of the protocol and received at least 2 months (8 weeks) of treatment:

- For **Arm A**: Nab-Paclitaxel + gemcitabine for 2 months followed by at least one course of FOLFIRI.3 (i.e. at least until alternation)
- **Arm B**: Nab-Paclitaxel + gemcitabine for 2 months

The main inclusion criteria were :

- Adenocarcinoma of the pancreas,
- Metastatic disease

Patients will be analyzed according to the treatment they actually received.

A list of patients excluded from the PP population will be provided, together with the reasons for their exclusion.

5.1.2 Population for tolerance analysis (SP)

It is defined as the ITT population having received at least one dose of chemotherapy (whatever the product). Patients will be analyzed according to the actual treatment received.

Tolerance criteria will be assessed for this population.

A list of patients excluded from the SP population will be provided, together with the reasons for their exclusion.

5.2 Definition of analysis subgroups

For exploratory purposes, the primary endpoint will also be analyzed in the subgroup of WHO 0-1 patients.

6 General information on statistical methods

Statistical analyses will be carried out by CRGA.

6.1 Software

Statistical analyses will be carried out using SAS software version 9.4 or later. Some graphs may be produced using R software version 2.11 or later.

6.2 Agreements concerning dates and durations

Time since randomization will be defined as the time elapsed since the day of randomization, with the day of randomization taken as day 1.

Time since start of treatment will be defined as the time elapsed since the day of the first treatment course, the day of the first treatment course being considered as day 1.

For this reason, durations are calculated using the following rule, for example for the time elapsed between death and randomization: day of death - day of randomization **+ 1**.

The day preceding the day of randomization (*resp.* the day preceding the day of treatment) will be considered as day -1 (day 0 does not exist).

The date of last news will default to the date of the last examination/monitoring performed.
The following conversion rules will be used to convert numbers of days into numbers of months or years: 1 month = 30.4375 days; 1 year = 365.25 days.

6.3 Missing data conventions

Except in the cases specified, missing data will not be replaced.

6.4 Baseline definition

Baseline measurements are the last measurements taken at randomization. In the event of missing data, the last measurement taken before the first treatment is used.

6.5 Statistics

Quantitative variables will be described using headcount, median, mean, standard deviation of the mean, minimum, maximum and inter-quartile range (Q1-Q3). Quantitative variables can be categorized using their median or a cut-off known from the medical literature.
Categorical variables will be described using percentages, and if necessary their bilateral 95% confidence intervals (calculated using the exact method).
Missing values are not taken into account when calculating frequencies and percentages.
The **confidence intervals** provided will be two-sided 95% confidence intervals, except for the main criterion where a one-sided 95% confidence interval will be given.
Survival data will be estimated and plotted using the Kaplan-Meier method (Kaplan and Meier, 1958).
This will be described by the median and rates calculated at different times. Two-sided 95% confidence intervals will be provided. Confidence intervals for rates will be constructed from the Greenwood variance calculated using the log-log transformation.
The median follow-up time is calculated using the reverse Kaplan-Meier method (Shemper, 1996).
For uni and multivariate analyses, hazard ratios will be estimated using a Cox model (Cox, 1984). The proportionality hypothesis will be tested using the graphical representation and residual-based test of Schöenfeld (Grambsch, 1994); the linearity of the effect of continuous variables on risk will be assessed using the graphical representation of martingale residuals. Confidence intervals for Cox model coefficient estimates will be calculated using Wald's method.
There are no statistical comparisons planned between the arms of this study, but the HR between the arms with their IC95% will be calculated, and statistical comparisons with the calculation of p-values may be made for exploratory purposes.

7 Statistical analysis

	ITT	ITTm	PP	SP
Eligibility	X	x	x	
Characteristics at randomization	X	x	x	
Main criterion				
Progression-free rate at 6M	X	X	X	
Secondary criteria				
Overall survival	X	x	x	
Progression-free survival	X	x	x	
Objective/best response rate	X	x	x	
Treatment administration		x	x	X
NCI-CTC toxicities				X
Neuro Toxicities mTNS				X
Quality of life	X			

7.1 Patient characteristics at inclusion

7.1.1 Eligibility

Patient eligibility for randomization will be verified and described by :

- Number and percentage of patients who met all inclusion criteria
- Number and percentage of patients who met all non-inclusion criteria
- Number and percentage of patients who met all criteria (inclusion and non-inclusion)

7.1.1 Stratification criteria

- WHO general status (0 *vs* 1 *vs* 2)
- Number of metastatic sites (1 *vs* >1)

7.1.2 Demographic characteristics

The following randomization characteristics will be described:

- Inclusion center (number of patients included per center - described *in total* only)
- Age (year)
- Gender (Male *vs* Female)

7.1.3 Clinical features

The following randomization characteristics will be described:

- BMI (kg/m) ^{2}
- EVA score
- Presence of morphine treatment (Yes *vs.* No)
- Presence of neurotoxicity at inclusion: described by grade and type of toxicity

7.1.4 Biological characteristics

The following randomization characteristics will be described:

- Hemoglobin (g/dL)
- PNN (/mm)^3
- Wafers (x10 /mm)^{33}
- Total bilirubin (≤ N *vs*]N-2.5N] *vs*]2.5N-5N] *vs* > 5N)
- Conjugated bilirubin (≤ N *vs*]N-2.5N] *vs*]2.5N-5N] *vs* > 5N)
- PAL (≤ N *vs*]N-2.5N] *vs*]2.5N-5N] *vs* > 5N)
- LDH (mmol/L)
- Albuminemia (g/dL)
- Lymphocytes (/mm)^3
- ALAT (≤ N *vs*]N-2.5N] *vs*]2.5N-5N] *vs* > 5N)
- ASAT (≤ N *vs*]N-2.5N] *vs*]2.5N-5N] *vs* > 5N)
- Leukocytes (/mm)^3
- TP (%)
- Calcium (mmol/L)
- Potassium (mmol/L)
- Sodium (mmol/L)

7.1.5 Disease-related characteristics

The following randomization characteristics will be described:

- Location of metastatic sites (liver, peritoneum, lung, bone, other)
- Primary surgery (Yes *vs.* No) and if yes, type of resection (R0 *vs.* R1 *vs.* R2)
- Presence of at least one previous treatment (Yes *vs* No) and if yes :
  - Neoadjuvant treatment (Yes *vs.* No) and if yes, listing of treatment types
  - Adjuvant treatment (Yes *vs.* No) and if yes, listing of treatment types

7.2 Follow-up features

The median follow-up time and its 95% confidence interval will be calculated in months, by treatment arm and in total.

7.3 Primary endpoint

7.3.1 Definition of primary endpoint

The primary endpoint was the rate of patients alive and progression-free 6 months after randomization.
Progression is assessed by the investigator and defined radiologically according to RECIST v1.1 criteria and/or clinically as deterioration in general condition unrelated to treatment, tumor masses palpable on clinical examination (adenopathies, tumor hepatomegaly, peritoneal carcinosis), pleural effusion, ascites.
Patients who progressed or died before 6 months will be considered to have failed the primary endpoint at 6 months.
The 6-month images will be the images taken at 6 months with a window of +/- 1 month.
Patients without a 6-month assessment will be reviewed according to the following rules:

- If the patient has a later assessment (7 months or more) and is not progressing at that date, he or she will be considered progression-free at 6 months.
- If the patient has documented progression at more than 6 months without imaging at 6 months, then this patient should be reviewed.

7.3.1 Evaluation of primary endpoint

The rate of patients alive and progression-free at 6M will be calculated by treatment arm with its one-sided 95% confidence interval.

7.4 Secondary efficacy criteria

7.4.1 Overall survival

7.4.1.1 Defining overall survival

It is defined as the time between the date of randomization and the date of death (whatever the cause). Patients lost to follow-up or alive at the time of analysis will be censored at the date of last news.

7.4.1.1 Assessment of overall survival

The time scale considered will be the month.
Overall survival will be plotted using the Kaplan Meier estimator for each treatment arm. Median survival and survival rates at 4, 8, 12, 18 and 24 months will be calculated, along with their 95% confidence intervals.
For the various OS tests, HRs (IC95%) between the 2 treatment arms will be calculated, and p values may also be calculated for exploratory purposes.

7.4.1 Progression-free survival

7.4.1.1 Defining progression-free survival

It is defined as the time between the date of randomization and the date of 1ère progression (clinical and/or radiological) or death (whatever the cause). Patients alive without progression at the time of analysis will be censored at the date of last news.

7.4.1.1 Assessment of progression-free survival

The time scale considered will be the month.
Progression-free survival will be plotted using the Kaplan Meier estimator. Median survival and rates at different time points will be calculated, along with their 95% confidence intervals.
For the various PFS tests, HRs (IC95%) between the 2 treatment arms will be calculated, and p-values may also be calculated for exploratory purposes.

7.4.1 Better response to treatment

7.4.1.1 Defining the best response

The best response rate is defined by treatment arm over the entire treatment.

The objective response rate is defined as the complete + partial response rate.
The disease control rate is defined as the complete + partial + stable response rate.

7.4.1.1 Evaluating the best response

The percentages of complete response, partial response, stable response, progression and non-evaluable response will be specified and described using standard statistics.
The best response rate will also be described in terms of objective response versus no objective response and disease control versus no control in each arm.

7.4.2 Survival to WHO >1

7.4.2.1 Definition

Survival to WHO >1 will be analyzed for each arm.
It is defined as the time between the date of randomization and the date of clinical evaluation when WHO is >1 or the date of death (whatever the cause). Living patients without WHO >1 at the time of analysis will be censored at the date of last news.

7.4.2.2 Evaluation

The time scale considered is the month.
Survival to WHO >1 will be plotted using the Kaplan Meier estimator. Median survival to WHO >1 and rates at different time points will be calculated, along with their 95% confidence intervals.
For the various tests of survival to WHO >1, the HR (IC95%) between the 2 treatment arms will be calculated for exploratory purposes.

7.5 Tolerance assessment

7.5.1 Chemotherapy administration

7.5.1.1 Treatment duration

The duration of treatment (converted into months) is calculated using the formula :

Start date of last administration - start date of first administration + 1 day

Temporary stoppages and any deferral days during this period will not be subtracted from this duration. It will be described using the usual descriptive statistics for each treatment arm.

7.5.1.2 Doses administered

The average number of cures will be postponed.
The cumulative average dose administered (over all courses of treatment) will be calculated in mg/m^2 for each type of treatment: 5FU Continu, irinotecan, Nab-paclitaxel, Gemcitabine.
The body surface area used will be that supplied by the investigator on the treatment form, otherwise, if it is not provided, it will be calculated using the Gehan and Georges formula:

$$0.0235 \times \text{height(cm)}^{0.42246} \times \text{weight(kg)}^{0.51456}$$

The weight used will be the weight indicated for the treatment in question. If the weight is missing, the non-missing weight from the previous treatment will be used instead. If no weight information is available, the weight at inclusion will be used.

The ratios of treatment doses received to theoretical doses will be described by type of treatment, using the usual descriptive statistics for each treatment arm.
The % of patients who received more than 80 and 90% of the theoretical treatment dose will be reported.

7.5.1.1 Dose modification

The number of patients with at least one dose modification will be described according to the usual descriptive statistics by arm and type of treatment.

7.5.1.2 Permanent cessation of treatment

The number and percentage of patients permanently discontinuing protocol treatment, and the reasons for discontinuing protocol treatment (% out of the number of patients discontinuing treatment) will be described using the usual descriptive statistics for each treatment arm.

7.5.1 Toxicities

Toxicities will be described during treatment and during post-treatment follow-up in the same way.
Toxicities (graded according to NCI-CTC v 4.0) will be described per treatment arm by :

- Total number of patients by maximum grade of toxicity, grouped by grade (grade 1-2 and grade 3-4 and grade 5)
- The number of patients and the maximum grade of toxicity achieved by grouping grades (grade 1-2 and grade 3-4 and grade 5) by SOC and type of toxicity.

Peripheral neuropathic toxicities (graded according to mTNS) will be described per treatment arm by :

- Total number of patients by maximum grade of toxicity (grade 1-2-3-4)
- Number of patients and maximum toxicity grade reached (grade 1-2-3-4) by toxicity type

7.5.1 EIG

A summary of all SAEs will be provided by pharmacovigilance.

7.6 Assessment of quality of life

The number of patients analyzable for QoL (having at least one questionnaire) and the percentage (out of the number of patients included) will be described.

7.6.1 Definition

It will be assessed using the QLQ-C30 questionnaire (version 3.0). The QLQ-C30 will be completed before randomization, then every month for the first 4 months, then every 2-3 months until progression or death.

This 30-item scale comprises 15 dimensions enabling 15 scores to be calculated: 5 functional ability scores (physical ability, ability to work or perform any household task, cognitive ability, emotional state, social state), a global quality of life score, a financial problems score and 8 symptom scores (fatigue, nausea/vomiting, pain, dyspnea, sleep disturbance, loss of appetite, constipation, diarrhea).

For the overall health score, time to definitive deterioration, defined as the time interval between the date of randomization and the date of a score decrease of more than 5 points (compared with the score at randomization) without subsequent improvement of more than 5 points, or death, or the date of last news, will be studied in an exploratory way. Living patients without a score decrease of more than 5 points will be censored at last news.

7.6.2 Evaluation

An estimate of the time to definitive deterioration of the global health score will be made using the Kaplan-Meier method, and compared, in an exploratory way, according to the treatment arm, by a Log Rank test.