PAS v2.0 framework applicable from 15/02/2020

RANDOMIZED PHASE II EVALUATION OF EFFICACY AND TOLERANCE OF 2 THERAPEUTIC STRATEGIES COMBINING BEVACIZUMAB WITH CHEMOTHERAPY: DE-ESCALATION VERSUS ESCALATION IN PATIENTS WITH UNRESECTABLE, NON-PRE-TREATED METASTATIC COLORECTAL CANCER

PRODIGE 45 - HIGHLIGHT

Statistical analysis plan

Final analysis

Version 2.0 of 25/11/2020

Editor: Karine Le Malicot

Review committee: Pr Jean-Marc Phelip, Lila Gaba, Francis Diedhiou, Emilie Barbier

Signature page

By signing this sheet, I agree to the statistical analysis plan:

Prof. Jean-Marc Phelip	Date	Signature
Coordinator		

Karine Le Malicot	Date	Signature
FFCD		
Biostatistician		

Emilie Barbier	Date	Signature
FFCD		
Independent statistician		

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Abbreviations :

RECIST	ResponseEvaluation Criteria In Solid Tumours
SSP	Survival without progression
SG	Overall Survival
TS	Thymidilate Synthase
ITT	Intent to treat
ITTm	Modified intention to treat
PP	Per protocol
SP	Safety Population
BMI	Body Mass Index
NOT	Systolic blood pressure
PAD	Diastolic blood pressure
SOC	System Organ Class
PT	Preferred Term

1 Introduction

1.1 Objectives of the trial

1.1.1 *Main objective*

The primary objective is to evaluate the rate of patients without strategy failure 16 months after randomization.

Strategy failure is defined by :

- Progression (defined in each arm)* using RECIST v1.1 criteria or
- Deaths (all causes) or
- Toxicity leading to permanent discontinuation of one of the chemotherapy products (oxaliplatin and irinotecan) or
- Patient's refusal to continue the strategy or
- Investigator's decision to discontinue strategy

*Progression is defined differently depending on the treatment arm because the two strategies are different:

- In the standard (climbing) arm, progression is considered a failure:

If it occurs during 1st chemotherapy with LV5FU2 + bevacizumab and 2nd chemotherapy with FOLFIRI + bevacizumab cannot be administered
if it occurs during 2nd chemotherapy with FOLFIRI + bevacizumab and if 3rd chemotherapy with FOLFOX + bevacizumab) cannot be administered e or if it occurs during 3rd chemotherapy

- In the experimental strategy (de-escalation), progression is considered a failure:

if it occurs during chemotherapy with modified FOLFOXIRI + bevacizumab or FOLFIRI + bevacizumab. Progression during treatment with capecitabine/LV5FU2 + bevacizumab does not constitute failure of the strategy.

1.1.2 *Secondary objectives*

The secondary objectives are:

- Best response according to RECIST version 1.1 at 16 months
- Time to best response during the strategy
- Time to strategy failure
- Progression-free survival (PFS) at 2 and 3 years over the course of the strategy
- Overall survival (OS) at 2 years and 3 years
- Tolerance of both strategies
- The dose intensity for each treatment and the duration of the strategy
- Quality of life (EORTC QLQ-C30)

1.1.3 *Objectives Biological ancillaries*

Organic :

- Demonstrate the impact of RAS mutations on response to bevacizumab in mRCC
- Demonstrating the impact of thymidilate synthase (TS) polymorphism
- Prospectively determine the frequency of tumor patients with low levels of mutated RAS alleles.
- Evaluate the use of a new, highly sensitive technique for determining RAS status in blood.
- Analyze the correlation between the level of mutated RAS alleles in the primary tumor and peripheral blood.
- Analyze changes in the rate of mutated RAS alleles over time.
- Assess circulating VEGF (at time of diagnosis and every 2 cures)

Imaging :

- Evaluate the relationship between PFS and tumor size at diagnosis
- Evaluate the relationship between PFS and visceral fat (measured by CT scan at inclusion)

2 Experimental design

2.1 Study diagram

This study is a phase II randomized non-comparative trial.

2.2 Treatment arms

In the standard arm or escalation strategy, patients will receive 1ère chemotherapy based on LV5FU2 or capecitabine + bevacizumab. After progression, they will receive 2ème chemotherapy with FOLFIRI + bevacizumab. After progression, they will receive 3ème chemotherapy with FOLFOX4 + bevacizumab.

When progression occurs during 3ème chemotherapy, or 3ème CT cannot be administered, patients will be treated according to the investigator's choice.

In the experimental arm or de-escalation strategy, induction treatment (4 cycles of FOLFOXIRI + bevacizumab followed by 4 cycles of FOLFIRI + bevacizumab) is followed by **maintenance** with (LV5FU2 or capecitabine) and bevacizumab until progression. After 1ère progression during maintenance treatment, the patient will be treated again with induction treatment (4 cycles of FOLFOXIRI + bevacizumab followed by 4 cycles of FOLFIRI + bevacizumab) followed by maintenance with capecitabine and bevacizumab until progression and so on.

If progression occurs during induction therapy (FOLFOXIRI + bevacizumab or FOLFIRI + bevacizumab), patients will be treated according to the investigator's choice.

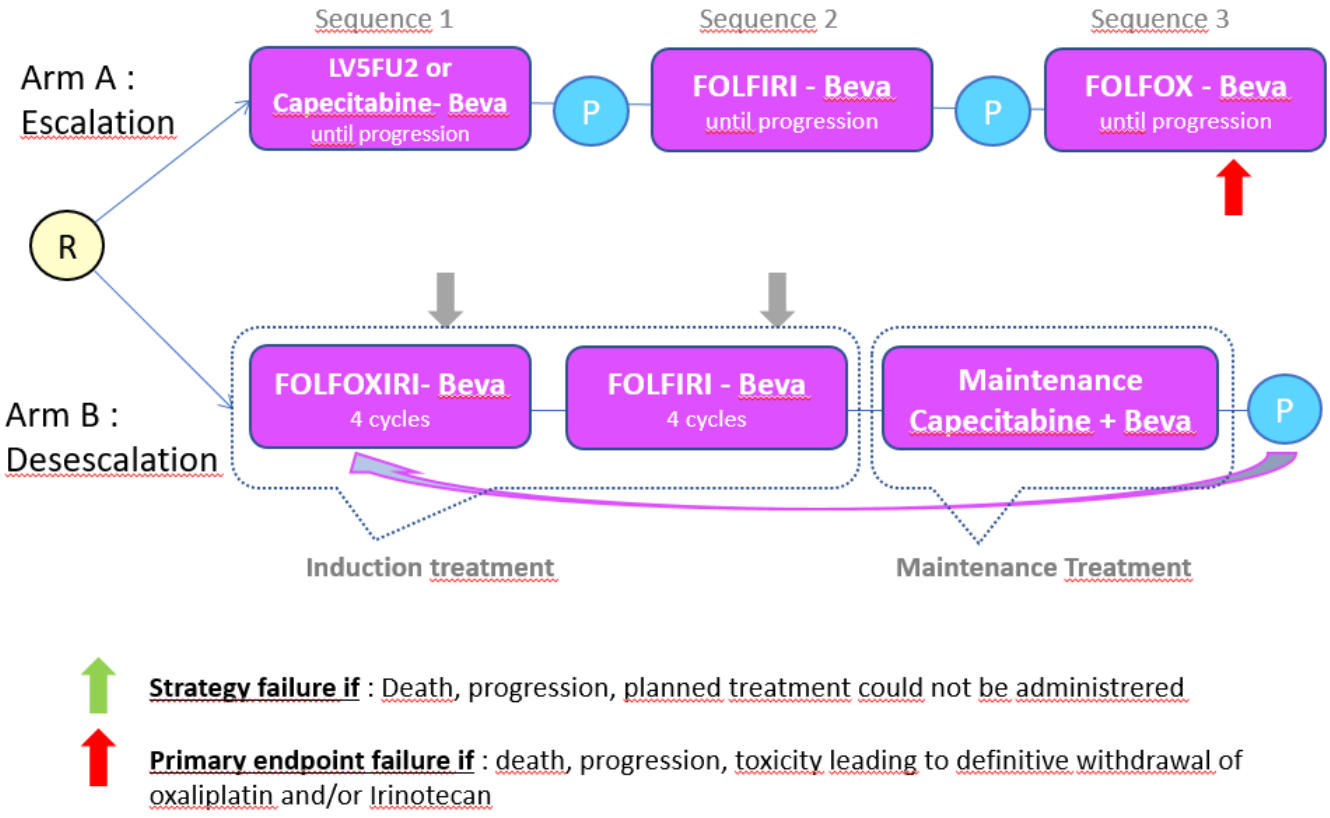
2.3 Randomization

Patients were randomized (1:1) using the minimization technique (Pocock and Simon (Biometrics, 1975)) according to the following stratification factors:

- Center
- WHO performance index 0/1 vs 2

2.4 Study diagram

The following diagram illustrates the patient follow-up process:



2.5 Number of subjects required

The clinical hypotheses for the study design were :

H_0 : A rate of 40% of patients alive and without strategy failure at 16 months is not interesting.

H_1 : A live patient rate without strategy failure at 16 months of 55% is expected.

With an α risk (one-sided) of 5% for a power of 80.85%, using the exact binomial method (R software), 75 patients were to be randomized to each strategy.

Taking into account that 10% of patients will not be evaluable for the mITT population, 84 patients per strategy will be randomized according to the 1:1 ratio.

The conclusion of the study was to be based solely on the experimental strategy according to the rule defined below and on the first 75 evaluable patients:

- If 38 or more patients do not fail the strategy at 16 months, the strategy is considered effective.

2.6 Trial planning/analysis history

The trial was stopped at 21 randomized patients because patient recruitment was slow and difficult. The last patient was randomized on April 10, 2018.

Follow-up of randomized patients has continued, and a final analysis will be carried out when all patients are off treatment.

3 Study populations for analysis

3.1 Intention-to-treat (ITT) population

All patients included in the study, regardless of inclusion or non-inclusion criteria, and analyzed according to the strategy assigned by randomization.

3.2 Modified intention-to-treat population (mITT)

All patients in the ITT population who received at least one dose of treatment (regardless of dose and treatment).

3.3 Per-Protocol (PP) population

Not applicable

3.4 Population for safety analysis (SP)

Not applicable. Safety analysis will be performed on the ITTm population.

4 General information on statistical analysis methods

4.1 Software

Statistical analyses will be carried out using SAS software version 9.4 or later and R.

4.2 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 first treatment administration, this day being considered as day 1.

As a result, durations are calculated using the following rule, for example for the time elapsed between death and inclusion: day of death - day of inclusion **+ 1**.

The day preceding the day of inclusion (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 be the date of the *last examination performed or the last treatment taken in the last follow-up/consultation.*

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.

4.3 Missing data conventions

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

In the event of partially missing date data, the following rules will apply

For a start date :

- if the day is missing (**UK/01/2012), the day will be set to "01".**
- if the month is missing (**UK/UK/2012), the date will be set to "01/01/2012".**

For an end date :

- if the day is missing (**UK/01/2012), the day will be set to "30" (although beware of February).**
- if the month is missing (**UK/UK/2012), the date will be set to "30/12/2012".**

For all other dates:

- if the day is missing (**UK/01/2012), the day will be set to "15".**
- if the month is missing (**UK/UK/2012), the date will be set to "15/06/2012".**

4.4 Baseline definition

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

4.5 Definition of analysis subgroups

Not applicable

5 General information on statistical analysis

Quantitative data will be described for each group and for the population as a whole, using the following descriptive statistics: headcount, mean, standard deviation, median, first and third quartile, minimum and maximum. These statistics

will be considered as the usual statistics for the analysis of quantitative variables. Quantitative variables can be categorized using their median or a cut-off known from the medical literature.

Categorical variables will be summarized for each group and for the population as a whole, using the following descriptive statistics: frequencies and percentages for each level of the variable. These statistics will be considered as the usual statistics for the analysis of categorical variables. Where necessary, confidence intervals for the proportions will be calculated.

For the primary endpoint, a two-sided 90% confidence interval will be calculated.

Survival is estimated for censored variables using the Kaplan Meier method (Kaplan and Meier, 1958). This will be described by the median and rates calculated at different times. 95% confidence intervals will be provided. Confidence intervals for rates will be constructed from the Greenwood variance calculated using the log-log transformation. For the median confidence interval, the upper bound will be defined as the smallest time for which the upper bound of the associated survival rate confidence interval, calculated using Greenwood's method, is less than or equal to 50%. Similarly, the lower bound will be the smallest time for which the lower bound of the confidence interval of the associated survival rate is less than or equal to 50%.

The median follow-up time is calculated using the reverse Kaplan-Meier method (Shemper, 1996).

Unless otherwise stated, **results will be described separately for each treatment arm**; thus, where "total number of patients" is specified, the total number of patients in the arm in question should be considered.

6 Statistical analysis

	ITT	**ITTm**
Eligibility	X	
Characteristics of the population at randomization	X	
Main criterion		
Failure-free rate at 16M	X	X
Secondary criteria		
Overall survival	X	X
Progression-free survival	X	X
Best answer	X	X
Time to best response	X	X
Time to strategy failure	X	X

Treatment administration		X
NCI-CTC toxicities		X
Quality of Life	X	

6.1 Patient characteristics at randomization

Patient characteristics at inclusion will be described by treatment arm and in total for the ITT population.

6.1.1 *Inclusion and non-inclusion criteria at inclusion*

A description of the stratification factors (described on the randomization sheet) and of the inclusion and non-inclusion criteria for each treatment arm will be carried out to ensure that the stratification factors are correctly distributed, but no statistical tests will be performed.

6.1.2 *Demographic characteristics*

The following characteristics at inclusion will be described using descriptive statistics:

- Age
- sex,

6.1.3 *Clinical and disease-related features*

The following characteristics at inclusion will be described using descriptive statistics:

- BMI (Kg/m^2)
- PAS (mmHg)
- PAD (mmHg)
- kRAS status
- nRAS status
- Delay between randomization and diagnosis
- Histological type
- Tumor size (mm)
- Location
- Resection of the primary tumor
- Adjuvant chemotherapy
- Length of illness
- Metastatic location
- The number of metastatic sites

6.1.4 *Biological characteristics*

The following characteristics at inclusion will be described using descriptive statistics:

- PNN (/mm)^3
- Inserts (*10 /mm)^{33}
- HB (g/dL)
- Leukocytes (/mm)^3
- Lymphocytes (/mm)^3
- TP (%)
- TCK (seconds) or TCA (ratio)
- PAL (IU/L)
- AST (UI/L)
- ALAT (UI/L)
- GGT (UI/L)
- LDH (UI/L)
- Albuminemia (g/L)
- Protidemia (g/L)
- Total bilirubin (µmol/L)
- Conjugated bilirubin (µmol/L)
- Calcium (mmol/L)
- Potassium (mmol/L)
- Magnesium (mmol/L)
- Sodium (mmol/L)
- Creatinine clearance (mL/min)
- Creatininemia (µmol/L)

6.2 Efficiency assessment

6.2.1 *Follow-up features*

The median follow-up time and its 95% confidence interval will be calculated in months using the inverted Kaplan-Meier method.

6.2.2 *Main criterion*

6.2.2.1 Definition of primary endpoint

The rate of patients without strategy failure at 16 months after randomization will be calculated on the basis of the investigator's assessment at 16 months +/- 30 days.

Strategy failure is defined by :

- Progression (defined in each arm) using RECIST v1.1 or
- Death (all causes) or
- Toxicity leading to permanent discontinuation of one of the chemotherapy products (oxaliplatin and irinotecan) or
- Patient's refusal to continue the strategy or
- Investigator's decision to discontinue strategy

Progression is defined differently depending on the treatment arm because the two strategies are different:

- In the standard arm (climbing), progression will be considered a failure:

If it occurs during 1st chemotherapy with LV5FU2 + bevacizumab and 2nd chemotherapy with FOLFIRI + bevacizumab cannot be administered
if it occurs during 2nd chemotherapy with FOLFIRI + bevacizumab and if 3rd chemotherapy with FOLFOX + bevacizumab) cannot be administered or if it occurs during 3rd chemotherapy

- In the experimental strategy (de-escalation), progression is considered a failure:

if it occurs during chemotherapy with modified FOLFOXIRI + bevacizumab or FOLFIRI + bevacizumab. Progression during treatment with capecitabine/LV5FU2 + bevacizumab does not constitute failure of the strategy.

6.2.2.2 Evaluation of primary endpoint

It will be described using a percentage and a one-sided 95% confidence interval per arm.

No conclusion on the primary endpoint can be drawn because the number of evaluable patients has not been reached.

6.2.3 ***Secondary efficacy criteria***

6.2.3.1 Best RECIST response

6.2.3.1.1 Definition

The best response to treatment is defined according to RECIST v1.1 criteria.
Imagery taken up to 1 month after stopping treatment and before starting another treatment will be taken into account.

6.2.3.1.2 Evaluation

Descriptive statistics will be presented by treatment arm according to the different categories: complete response, partial response, stability, progression or non-evaluable.

6.2.3.2 Time to best answer

6.2.3.2.1 Definition

Time to best response is the time between the date of randomization and the date of the first best response scan to the strategy.

6.2.3.2.2 Evaluation

Descriptive statistics will be presented for each treatment arm.

6.2.3.3 Time to strategy failure

6.2.3.3.1 Definition

Time to strategy failure is the time between the date of randomization and the date of strategy failure.

6.2.3.3.2 Evaluation

Descriptive statistics will be presented for each treatment arm.

6.2.3.4 Overall Survival (OS)

6.2.3.4.1 Definition

Overall Survival (OS) is defined as the time between the date of randomization and the date of death (whatever the cause). For living patients, the time will be calculated between the date of randomization and the date of last news.

6.2.3.4.2 Criterion evaluation

The time scale considered is the year.
Overall survival will be plotted using the Kaplan Meier estimator, and live patient rates will be given at different time points, along with their 95% confidence intervals, and presented by treatment arm.

6.2.3.5 Progression-free survival

6.2.3.5.1 Definition

Progression is defined as radiological progression according to RECIST v1.1 criteria and/or clinical progression or death. Time is defined as the time between the first progression or death and the date of randomization. For patients alive and progression-free, time is calculated from the date of randomization to the date of last news.

6.2.3.5.2 Evaluation

The time scale considered is the year.
Progression-free survival will be plotted using the Kaplan Meier estimator, and rates of live patients will be given at different time points, along with their 95% confidence intervals, and presented by treatment arm.

6.3 Tolerance assessment

6.3.1 *Treatment administration*

The duration of treatment for each chemotherapy and the total duration of the strategy will be described using descriptive statistics. The dose intensity of each treatment will be described.

The dose intensity of each treatment and the duration of the strategy will be described. The duration of the strategy will be calculated as the time between the date of the first treatment course and Day 1 of the last course (+ 14 days if the patient is receiving 5FU IV or + 21 days if the patient is receiving capecitabine).

6.3.2 *Toxicities*

Toxicities will be described by treatment arm and treatment causality (related/doubtful versus unrelated) according to NCI-CTC version **4.0** criteria by :

- toxicities over all cycles will be summarized according to maximum grade per soc/ preferred term for each patient.
- the number (%) of patients with at least one maximum grade 1-2 and 3-4-5 toxicity by type (SOC and PT);
- number (%) of patients with maximum grade 1-2 and 3-4-5 toxicity, all types combined

In addition, the following events of particular interest will also be described: hypertension, proteinuria, gastrointestinal perforation, abscesses and fistulas, wound healing complications, hemorrhages, arterial thromboembolic events, venous, posterior reversible encephalopathy syndrome, congestive heart failure, fistulas and non-gastrointestinal abscesses.

A list of grade 5 toxicities will be provided.

6.3.3 *Serious adverse events*

The FFCD's pharmacovigilance department will provide a summary of all SAEs.

6.4 Quality of life analyses

Quality of life will be assessed using the QLQ-C30 questionnaire. Questionnaires are completed before inclusion and during the study.

The QLQ-C30 questionnaire comprises 30 items, with 15 dimensions and 15 scores to calculate: 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).

6.4.1 *Descriptive analysis*

A description of the number of patients in the following categories by treatment arm will be provided:

- Having a baseline questionnaire
- With at least one follow-up questionnaire
- Having a baseline questionnaire and at least one follow-up questionnaire

For follow-up questionnaires, a table showing the number of questionnaires per treatment arm will be presented, in particular to validate whether the score analyses described below make sense.

6.4.2 ***Analysis of scores and time to final deterioration***

For the QLQ-C30 scores of overall health, physical ability, cognitive ability and fatigue, longitudinal evolution will be studied, along with the percentage of symptomatic progression, defined as the percentage of patients with a score reduction of at least 5 points compared with inclusion, with no subsequent improvement.
For the global health score, time to definitive deterioration will also be studied, 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 inclusion) without subsequent improvement of more than 5 points, or death, or the date of last news. Living patients without a score decrease of more than 5 points will be censored at last news.

6.4.2.1 Evaluation

Survival to definitive deterioration of overall health score will be estimated using the Kaplan-Meier method.

6.5 Additional analyses

Not applicable

6.1 Ancillary analyses

The ancillary analyses provided for in the protocol will be the subject of one or more statistical analysis plans.

7 Third-party validation of analyses

No analysis validation is planned, since the analyses will be descriptive only.