



**Efficacy and safety of Aflibercept in combination with FOLFIRI chemotherapy
as first-line treatment in patients with metastatic colorectal cancer**

Phase II single-arm - multicentric

FFCD 1302

Statistical Analyses Plan

Final Analysis

Version : 3.0

Date : 14 September 2018

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1 Introduction

1.1 Study objectives

The objective of the study was to evaluate the efficacy and safety of a first-line combination of FOLFIRI chemotherapy and afibbercept in patients with metastatic colorectal cancer (mCRC).

1.1.1 Main objective

The main objective is to evaluate the rate of 6-months progression-free patients (RECIST version 1.1) according to the investigator.

1.1.2 Secondary Objectives

The secondary objectives of the study are :

- Overall survival: median and rates at 2, 4, 6, and 12 months;
- Progression-free survival: median and rates at 2, 4, 6, and 12 months;
- Rate of progression-free patients at 6 months according to the centralized review.
- Time to progression
- Objective response rate at 2, 4, 6 and 12 months
- Disease control rates at 2, 4, 6 and 12 months
- Best tumor response
- Duration of disease control (RC, RP, SD)
- Duration to objective response (RC, RP)
- Toxicity evaluated using the NCI-CTCAE scale version 4.0
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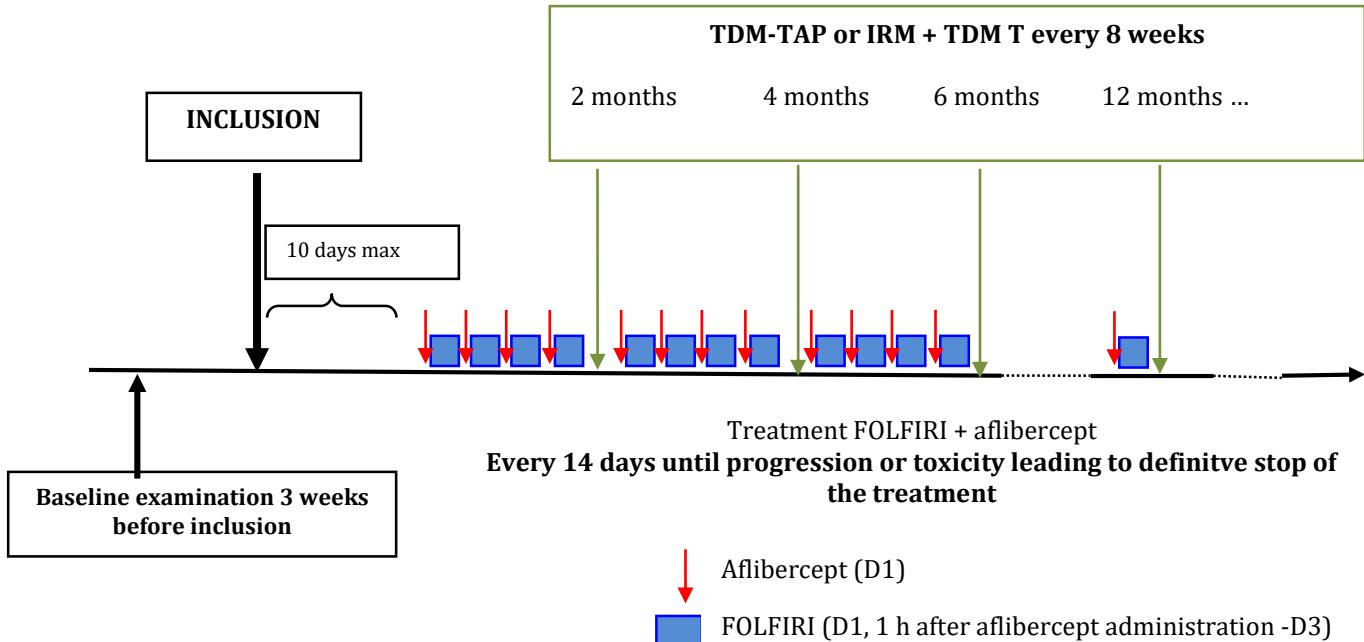
1.1.3 Exploratory study

Variation of cytokines and immunoregulatory cells during treatment (ancillary study).Plan expérimental

1.2 Study Schema

This is an open-label, Phase II, single-arm, multi-center trial.

1.3 Chronological sequence



1.4 Sample Size justification

The endpoint was the rate of 6-months progression-free patients and the assumptions were as follows :

H0: rate of 6-months progression-free patients of 55% or less is insufficient;

H1: rate of 6-months progression-free patients greater than 55% would justify the efficacy of the treatment; a rate of 75% is hoped for.

With a risk of one-sided alpha error of 5% and a power of 90%, using Simon's 2-step method (Minimax), it was required to include 49 patients. With a 10% rate of patients lost to follow-up, 54 patients were to be included.

1.5 Study steps

1.5.1 First step : Interim analysis

The interim analysis was performed in April 2017 and resulted in the termination of the study inclusions for non-effective treatment.

1.5.2 Second Step : Final Analysis

Non applicable

1.5.3 Transition between the 2 stages

Non applicable



1.6 Analyses study planning.

- The stage I analysis was performed after the inclusion of the 33rd patient and a minimum follow-up of 6 months, i.e. in April 2018. It was recommended to stop the inclusions.
- The final analysis is based on the 40 patients included in the study.

1.7 Ajustments

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

2 Study Populations

2.1 Definition

2.1.1 Intent-to-treat population (ITT)

The intent-to-treat population is defined as all patients included in the study, regardless of eligibility criteria and treatment received.

2.1.2 Modified Intent-to-treat population (mITT)

The modified intent-to-treat population is defined as all patients included in the study, regardless of eligibility criteria and treatment received, with at least a radiological evaluation during the 6 months of treatment.

3 Statistical methods generalities

Statistical analyses will be carried out by the CRGA.

1.1 Softwares

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

3.1 Conventions for dates and durations

The time since inclusion will be defined as the time elapsed since the day of inclusion, the day of inclusion being considered as day 1.

Therefore, the durations will be calculated using the following rule, for example for the time from death to inclusion: day of death - day of inclusion + 1.

The day before the day of inclusion (resp. the day before the day of treatment) will be considered as day -1 (day 0 does not exist).

The last news date will be the date of the last examination performed or the last treatment or consultation.



The following conversion rules will be used to convert the number of days to the number of months or years: 1 month = 30.4375 days; 1 year = 365.25 days.

3.2 Conventions for missing data

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

3.3 Baseline definition

Baseline measurements will be the last measurements taken before inclusion. In the event of missing data, the last measurement taken before the first administration of treatment will be retained.

3.4 Statistiques

The confidence intervals provided will be one-sided 95% confidence intervals.

Quantitative data will be described for the entire population, using the following descriptive statistics: population size, mean, standard deviation, median, first and third quartile, and minimum and maximum. These statistics will be considered standard statistics for the analysis of quantitative variables. Quantitative variables may be categorized using their median or a known cut-off from the medical literature.

Qualitative variables will be summarized for the entire population, using the following descriptive statistics: number, frequencies and percentages for each level of the variable. These statistics will be considered as the usual statistics for the analysis of qualitative variables.

Where necessary, confidence intervals for proportions will be calculated using the exact binomial law.

For survival data :

After description of the number of events, overall survival, survival in progression, time to progression, and time to objective response will be estimated using the Kaplan Meier method, then described by curves, by medians of survival, and rates at different temporalities, with their 95% confidence intervals. The confidence intervals for the rates will be constructed from the Greenwood variance calculated using the log-log transformation.

The median follow-up time will be estimated by the inversed Kaplan-Meier method (Shemper, 1996).

4 Statistical Analyses

1.1 Final Analysis

	ITT Population	mITT Population
Inclusion eligibility	XX	
Demographics data	XX	
Clinical data	XX	
Biological data	XX	
Disease characteristics	XX	
Follow-up time	XX	
Main criterion : Rate of patients alive and without progression at 6 months		XX
Rate of patients alive and without progression at 6 months (centralized review)		XX
Overall survival	XX	
Progression-Free survival	XX	
Time until progression	XX	
Objective response rate	XX	
Disease control rate	XX	
Disease control duration	XX	
Best response	XX	
Treatment administration		XX
Toxicities		XX

4.1 Baseline patients's characteristics

Number of patients making up each population (ITT, mITT) will be presented.

4.1.1 Eligibility

Population : ITT

Patient eligibility for inclusion will be described by :

- The number and percentage of patients meeting each inclusion criterion
- Number and percentage of patients who met all inclusion criteria
- Number and percentage of patients meeting each non-inclusion criterion
- Number and percentage of patients who met all non-inclusion criteria
- Number and percentage of patients who met all inclusion and non-inclusion criteria



4.1.2 Demographic data

Population : ITT

Clinical characteristics will be described ::

- Age (years) ;
- Center (Number of patients by center) ;
- Gender (Male vs Female).

4.1.3 Clinical characteristics

Population : ITT

Clinical characteristics will be described ::

- Height (cm) ;
- Weight (kg) ;
- General statel OMS (0 vs 1 vs 2) ;
- Arterial pressure

4.1.4 Biological characteristics

Population : ITT

Biological characteristics will be described ::

- Hb (g/dL) ;
- PNN neutrophiles (/mm³) ;
- Platelets (10³/ mm³) ;
- Total Bilirubin (μmol/L) ;
- Creatinine Clearance (mL/min) ;
- PAL ('≤Normal' vs '>Normal - <3*Normal' vs '≥ 3*Normal - <5*Normal' vs '≥5*Normal')
- ASAT ('≤Normal' vs '>Normal - <3*Normal' vs '≥ 3*Normal - <5*Normal' vs '≥5*Normal')
- ALAT ('≤Normal' vs '>Normal - <3*Normal' vs '≥ 3*Normal - <5*Normal' vs '≥5*Normal')
- GGT ('≤Normal' vs '>Normal - <3*Normal' vs '≥ 3*Normal - <5*Normal' vs '≥5*Normal')
- Proteinuriare (<2+ vs ≥2+)
- Leucocytes (/mm³) ;
- TP (%) ;
- Calcemia (mmol/L) ;
- LDH (UI/L) ;
- CEA (μg/L).

4.1.5 Disease characteristics

Population : ITT

Disease characteristics will be described ::

- Statut K-RAS, N-RAS and B-RAF (Wild-Type vs Mutated vs Not done) ;



- Patient under AVK (No vs Yes) ;
- Disease diagnostic (Primitive tumour vs Metastasis) ;

If Primitive tumour :

- Localization (Colon vs Rectum) ;
- Resection (No vs Yes) ; If Yes, type of resection (R0 vs R1 vs R2) ;

If Metastasis :

- Number of localization ;
- Total number of metastases ;
- Localization (Liver vs Lung vs Bone vs Other) ;
- For each localization : Resection (No vs Yes) ; If Yes, type of resection (R0 vs R1 vs R2) ;

- Adjuvant treatment (No vs Yes) ;

If Yes :

- Schema ('Chemotherapy vs 'Chemotherapy + biotherapy' vs 'Chemotherapy + Radiotherapy vs 'Other treatment') ;
- Number of cycles ;

4.2 Follow-up

A patient without an assessment for more than 12 months will be considered lost to follow-up.

4.2.1 Median time follow-up definition

Population : ITT

Median follow-up time is defined as the time interval between the inclusion date and the date of last news or date of death (regardless of cause).

Patients lost to follow-up or alive at the time of analysis will be censored as of the last reported date.

4.2.2 Evaluation

The median follow-up time, as well as its 95% confidence interval, will be calculated. It will be estimated by the reverse Kaplan Meier method.

4.3 Main criterion

Population : ITT

Definition of the main judgment criterion :

The primary endpoint is the rate of alive patients without progression (as assessed by the investigator) 6 months after inclusion.

Progression is defined by :

- Progression assessed by CT scan, according to the RECIST version 1.1 criteria;
- Death from any cause.

Patients without an assessment at 6 months will be reviewed according to the following rules:



- If the patient has a later evaluation (7 months or more) and is not progressing at that time, then the patient will be considered progression-free at 6 months;
- If the patient presents a documented progression within 2 months of the 6 month assessment then the patient will be considered to be progressing at 6 months. If the progression is documented beyond 8 months then the patient will not be considered progressive at 6 months;
- If a progression is documented prior to the 6-month assessment, the patient is considered progressive at 6 months.

4.3.1 Evaluation

The primary endpoint will be described with usual statistics.

Exploratory Analysis of the Primary Endpoint: The primary endpoint will be assessed on the total number of patients included in the study (ITTm). A one-sided 95% confidence interval will be calculated.

4.4 Secondary efficacy criteria

4.4.1 Rate of patients alive without progression

Population : mITT

4.4.1.1 Definition

It is defined as the number of patients alive without progression at 6 months in centralized review.

Progression is defined by :

- The progression evaluated by CT scan in centralized review, according to the RECIST version 1.1 criteria;
- Death, whatever the cause.

Patients without imagery at 6 months will be reviewed according to the following rules:

- If the patient has an imagery later (7 months or more) and is not progressing at this date, then the patient will be considered progression-free at 6 months;
- If the patient presents a documented progression within 2 months of the 6 months then the patient will be considered to be progressing at 6 months. If the progression is documented beyond 8 months then the patient will not be considered progressive at 6 months;
- If a progression is documented prior to the 6-month assessment, the patient is considered progressive at 6 months.

4.4.1.2 Evaluation

The endpoint will be described with usual statistics.

4.4.2 Overall survival

Population : ITT



4.4.2.1 Definition

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

4.4.2.2 Evaluation

Time scale considered will be the month.

Overall survival will be plotted using the Kaplan Meier estimator; median survival and rates at 2, 4, 6 and 12 months will be calculated with their 95% confidence intervals.

4.4.3 Progression-free survival

Population : ITT

4.4.3.1 Definition

It is defined as the delay between the inclusion date and the date of first radiological progression as assessed by the investigator according to RECIST version 1.1 criteria or the date of death (whatever the cause). Alive patients without radiological progression will be censored at the date of last news.

4.4.3.2 Evaluation

Time scale considered will be the month.

Progression-free survival will be plotted using the Kaplan Meier estimator; median survival and rates at 2, 4, 6 and 12 months will be calculated with their 95% confidence intervals.

4.4.4 Time until progression

Population : ITT

4.4.4.1 Definition

It is defined as the time between the inclusion date and the date of progression as assessed by the investigator according to the RECIST criteria version 1.1.

4.4.4.2 Evaluation

Time scale considered will be the month.

The endpoint will be described with usual statistics.

4.4.5 Objective response rate at 2, 4, 6 and 12 months

Population : ITT

4.4.5.1 Definition

Objective Response (OR) is defined as the number of Partial Response (PR) or Complete Response (CR) patients evaluated by the investigator according to the RECIST version 1.1 criteria.

The OR rate will be calculated at 2, 4, 6 and 12 months and described as follows:

- Objective response ;
- Stability



- Progression
- Not evaluable

4.4.5.2 Evaluation

The endpoint will be described at each time with usual statistics.

4.4.6 Time until objective response

Population : ITT

4.4.6.1 Definition

Objective Response (OR) is defined as the number of Partial Response (PR) or Complete Response (CR) patients evaluated by the investigator using RECIST version 1.1 criteria.

The time to objective response is defined as the time between the inclusion date and the date of first OR.

4.4.6.2 Evaluation

Time scale considered will be the month.

The endpoint will be described with usual statistics.

4.4.7 Rate of disease control

Population : ITT

4.4.7.1 Definition

Disease control is defined as the number of patients in Partial Response (PR) or Complete Response (CR) or Stability (S) as assessed by the investigator using the RECIST version 1.1 criteria.

The disease control rate will be calculated at 2, 4, 6 and 12 months and described as follows:

- Disease Control ;
- Progression
- Not Evaluable

4.4.7.2 Evaluation

The endpoint will be described at each time with usual statistics.

4.4.8 Disease control duration

Population : ITT

4.4.8.1 Definition

Disease control is defined as the number of patients in Partial Response (PR) or Complete Response (CR) or Stability (S) as assessed by the investigator using the RECIST version 1.1 criteria.

Duration of disease control is defined as the time from the inclusion date to the date of first progression in patients with Complete Response, Partial Response, or Stability (S) as assessed by the investigator using RECIST criteria version 1.1. If no progression, then the date of death is taken, or if the patient is alive, the last reported date.



4.4.8.2 Evaluation

Time scale considered will be the month.

The endpoint will be described with usual statistics.

4.4.9 Best response

Population : ITT

4.4.9.1 Definition

Best response is derived from the imagery evaluation

4.4.9.2 Evaluation

The endpoint will be described with usual statistics.

4.5 Safety Evaluation

Population : mITT

Safety will be evaluated :

- Duration of treatment, doses administered, modification of treatment doses ;
- Toxicities, collected after each treatment and described according to NCI-CTC version 4.0 criteria;

4.5.1 Treatment administration

4.5.1.1 Treatment duration

The duration of treatment will be calculated by the formula :

$$\text{Date of D1 last cycle} - \text{date of D1 first cycle} + 1$$

The time scale considered will be the month and will be described according to the usual descriptive statistics.

4.5.1.2 Doses administered

The number of cures will be described according to the usual descriptive statistics.

The ratio "administered dose / theoretical dose x 100" will be calculated for each treatment and described according to the usual descriptive statistics.

- The theoretical dose of Aflibercept is 4 mg/kg;
- The theoretical dose of Irinotecan is 180 mg/m²;
- The theoretical dose of 5FU Bolus is 400 mg/m²;
- The theoretical dose of 5FU Continuous is 2400 mg/m².

4.5.1.3 Doses modification

The change in dose will be described by :

- The number of patients with at least one reduced dose for at least one treatment;
- Reason for dose reduction



- Dose changes will be described by treatment and according to the usual descriptive statistics.

4.5.1.4 G-CSF administration

The G-CSF administration will be described by :

- Patients with at least one administration of G-CSF ;
- Type of administration (primary vs. secondary) ;
- The product administered

4.5.1.5 Treatment stop and further lines

Stop of the protocol treatment and the causes of treatment stop will be described (number, %).

A list of other causes of discontinuation will be provided.

The number of patients who have benefited from a subsequent line and subsequent treatments will be described.

4.5.2 Toxicities

Toxicities will be described according to NCI-CTC Version 4.0 criteria by :

- The number and percentage of patients with at least one toxicity out of all cycles by grade;
- The number of patients by grade and by SOC and preferred term;

4.5.3 SAE and deaths

A synthesis of the SAEs will be provided by pharmacovigilance.

4.6 Exploratory analyses

Not Applicable