PHASE II STUDY EVALUATING THE EFFICACY AND TOLERABILITY OF REGORAFENIB IN PATIENTS 70 YEARS AND OLDER WITH METASTATIC COLORECTAL ADENOCARCINOMA

Phase II non randomized

FFCD 1404 - REGOLD

Statistical Analyses Plan

Final Analyses

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1 Introduction

1.1 Objectives

1.1.1 Main objective

The primary objective of this study is to evaluate the tumor control rate (defined as the number of patients without progression, i.e., with complete response, partial response, or stability) under regorafenib treatment, according to the investigator (RECIST v1.1), 2 months after the start of treatment.

1.1.2 Secondary objectives

Secondary objectives are :

- 1-year Overall Survival
- 1-year Progression-Free survival
- Disease control at 2 months (centralized review)
- Objective response evaluated according to best response under treatment
- Time to therapeutic failure
- Time to autonomy degradation
- Time to quality of life deterioration
- Geriatric prognostic and predictive parameters
- Dose-intensity and its correlation to disease control
- Safety of regorafenib (NCI-CTC AE version 4.0)

1.1.3 Exploratory studies

The objective is to search for predictive factors of response and progression-free survival under regorafenib treatment. An analysis of the evolution of geriatric parameters during the follow-up will also be performed.Plan expérimental

1.2 Study design

Phase II open-labelled study , multicenter

1.3 Treatment

The dose of regorafenib is 160 mg (4 x 40 mg tablets) taken orally daily (21 days of treatment and 7 days without treatment, i.e. 28-day cycles).

1.4 Sample Size calculation

Clinical hypotheses are based on data from the CORRECT study and are as follows:

H_0: A tumor control rate at 2 months after the start of treatment of 25% or less is not sufficient.

H_1: A tumor control rate at 2 months after the start of treatment of more than 25% is considered sufficient. A rate of 47% is expected.

With a one-sided risk α of 5% and power of 90%, 42 patients are needed.

Patients who stop the study before documented tumor progression at 2 months will be considered non-responders for the primary endpoint analysis.

The decision rules after inclusion of 42 patients are:

- If 15 or fewer patients have a complete or partial response or stability then the treatment will be considered non-effective.
- If 16 or more patients have a complete or partial response or are stable, then the treatment will be considered effective.

1.5 Analyses planning

Analyses will be done once

1.6 Adjustments

Adjustments may be made to this analyses 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.

2 Study populations

2.1 Analyses populations

2.1.1 Intent-to-treat population (ITT)

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

2.1.2 Modified Intent-to-treat population (ITTm)

The modified intention-to-treat population is defined as all patients included in the study who received at least one regorafenib tablet and had at least one imaging assessment under protocol treatment.

2.1.3 Safety population (PT)

The safety population is defined as all patients included in the study who received at least one regorafenib tablet.

3 Statistical Generalities

Analyses will be done by CRGA.

3.1 Software

Statistical analyses will be performed with SAS software version 9.4. Some graphs can be made with R software version 2.11 or later.

3.2 Conventions

Time since inclusion will be defined as the time elapsed since the day of inclusion, with the day of inclusion being considered as day 1.
Therefore, the durations will be calculated according to the following rule, e.g. 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 date of last news will be the date of the last examination performed or the last treatment or the last medical consultation/visit.
The following conversion rules will be used for the conversion of the number of days to months or years: 1 month = 30.4375 days; 1 year = 365.25 days.

3.3 Conventions for missing data

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

3.4 Baseline definition

Baseline measurements will be the last measurement taken prior to inclusion or the last measurement taken prior to the first administration of treatment.

3.5 Statistics

The confidence intervals provided will be two-sided 95% confidence intervals except for the primary criterion where the calculated confidence interval will be a one-sided 95% confidence interval.

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

Categorical variables will be summarized using the following descriptive statistics: the number, frequencies and percentages for each level of the variable. These statistics will be considered the usual statistics for the analysis of categorical variables.
When necessary, the 95% confidence intervals for the proportions can be calculated from the exact binomial distribution.

Survival data will be estimated and plotted using the Kaplan Meier method (Kaplan and Meier., 1958). They will be described by the median and rates calculated at different time points with their two-sided 95% confidence intervals. Confidence intervals for the rates will be constructed from the Greenwood variance calculated using the log-log transformation.

Median follow-up time will be estimated using the inverse Kaplan-Meier method (Shemper, 1996).

As an exploratory measure, for uni and multivariate analyses, the hazard ratios will be estimated using a Cox model (Cox, 1984). The hypothesis of proportionality of the rates will be tested using the graphical representation and the test based on Schöenfeld's residuals (Grambsch, 1994); the linearity of the effect of the continuous variables on the risk will be evaluated from the graphical representation of the martingale residuals. Confidence intervals for the coefficient estimates of the Cox models will be calculated using the Wald method.

4 Analyses statistiques

	ITT Population	ITTm Population	Population de tolérance
Baseline description			
Eligibility	X		
Demographics	X		
Clinical characteristics	X		
Biological characteristics	X		
Disease characteristics	X		
Main criterion			
Tumoral control	X		
Critères secondaires			
Follow-up time	X		
OS, PFS	X		
Tumoral control (Centralised review)	X		
Objective response	X		
Time to therapeutic failure	X		
Time to autonomy deterioration	X		
Time to QOL deterioration	X		
Safety			
Treatment			X
Toxicities			X

4.1 Baseline characteristics

4.1.1 Eligibility

Population : ITT

Patient eligibility at inclusion will be described by:

- The 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 inclusion and non-inclusion criteria

4.1.2 Demographics

Population : ITT

Following characteristics will be described :

- Age (years) ;
- Number of patients per center ;
- Sex

4.1.3 Clinical characteristics

Population : ITT

Following characteristics will be described :

- Weight (kg) ;
- ECOG (0 *vs* 1) ;
- Geriatric assessment (yes/no) before starting treatment
- ADL and IADL
- Köhne Score

Definition :

Low :

- OMS 0-1 and only one metastatic site

Intermediate :

- OMS 0-1 and more than one metastatic site and PAL ≤ 300 U/L
- OMS >1 and white blood cells ≤ 10 x 10^9/L and only one metastatic site

High :

- OMS 0-1 and more than one metastatic site and PAL > 300 U/L
- OMS >1 and white blood cells > 10 x 10^9/L
- OMS >1 and white blood cells ≤ 10 x 10^9/L and more than one metastatic site

4.1.4 Biological characteristics

- Haemoglobin (g/dL)
- Creatinin (µmol/L)
- PAL (Ul/L)
- Leucocytes (/mm^3)
- CEA (µg/L)

4.1.5 Disease characteristics

Population : ITT

Following characteristics will be described :

- Time between primary tumor diagnosis and study inclusion (months)
- Time between metastatic diagnosis and study inclusion (months)
- Primary tumor Localization
- Primary tumor resection
- Metastatic localization
- BRAF status
- RAS status
- MSI/MSS status
- Previous treatment and description

4.2 Follow-up

4.2.1 Definition

Population : ITT

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

4.2.2 Evaluation

The median follow-up time (for alive patients) and its 95% confidence interval will be calculated in months. It will be estimated by the inverse Kaplan Meier method.

4.3 Main efficacy criterion

Population : ITTm

4.3.1 Definition

The primary endpoint is to evaluate the tumor control rate. It is defined as the percentage of patients with a complete, partial or stable tumor response 2 months after the start of treatment according to the investigator's RECIST v1.1 criteria.

Patients who stopped treatment (due to radiological progression or death) before 2 months after the start of treatment will be considered as having failed tumor control. Discontinuations for other causes will be reviewed on a case-by-case basis; verify that the patient has not taken any subsequent treatment between the date of discontinuation and the date of imaging. In case of clinical progression, if no imaging is available, the patient will be considered to have failed tumor control; otherwise, review the medical record to determine the reason for the clinical progression.

If imaging at 2 months is not available but imaging before 2 months is done then:

- Patients with radiological and/or clinical progression on a previous evaluation will be considered to have failed tumor control at 2 months.
- Patients who have died (regardless of cause) before 2 months will be considered to have failed tumor control.

If 2-month imaging is not available, subsequent imaging will be reviewed if available and the patient record will be reviewed.

4.3.2 Evaluation

The primary endpoint will be assessed on the ITTm population. This criterion will be described according to the usual descriptive statistics. A one-sided 95% confidence interval will be calculated using the exact method.

The decision rules to be applied on 42 patients evaluable during the analysis (ITTm population) are :
- If 15 or less patients have a complete or partial response or stability, then the treatment is judged not effective.
- If 15 or more patients have a complete or partial response or are stable, then the treatment is considered effective.

These may be adjusted based on the actual number of evaluable patients included.

4.4 Secondary efficacy criteriaa

4.4.1 Overall Survival

4.4.1.1 Definition

It is defined as the time interval between the date of inclusion and the date of death (regardless of cause).

Patients lost to follow-up or alive at the time of analysis will be censored at the date of last news. A minimum follow-up of 1 year for the last included patient is required.

4.4.1.2 Evaluation

The time scale considered will be the month.

Overall survival will be plotted using the Kaplan Meier estimator and survival rates at different time points (3, 6, 9, 12 and 18 months) will be calculated along with their 95% confidence intervals.

4.4.2 Tumoral control (centralised review)

4.4.2.1 Definition

It is defined as the percentage of patients with a complete, partial, or stable tumor response at 2 months after the start of treatment as assessed by centralized review according to RECIST v1.1 criteria.

Patients who have stopped treatment before the 2-month assessment will be considered as having failed tumor control.

4.4.2.2 Evaluation

This criterion will be described according to the usual descriptive statistics. A one-sided 95% confidence interval will be calculated using the exact method.

4.4.3 Objective response

4.4.3.1 Definition

It is defined as the percentage of patients in objective response, i.e., complete response (CR) or partial response (PR) as assessed by the investigator according to RECIST v1.1 criteria. The objective response will be determined from the best response during treatment assessments. Patients who discontinue treatment without response assessment will be considered as having no objective response.

4.4.3.2 Evaluation

Objective tumor response rates will be described according to standard descriptive statistics.

4.4.4 Time to therapeutic failure

4.4.4.1 Definition

It is defined as the time between the date of inclusion and the date of treatment discontinuation (regardless of cause). Living patients without treatment discontinuation will be censored at the date of last treatment administration.

4.4.4.2 Evaluation

The time scale considered will be months.

The time to treatment failure will be plotted using the Kaplan Meier estimator and the rates at 6, 9, 12, 18 months will be calculated along with their 95% confidence intervals.

4.4.5 Progression-Free Survival

4.4.5.1 Definition

Elle est définie comme l'intervalle de temps entre la date d'inclusion et la date de 1ère progression radiologique et/ou clinique selon l'investigateur ou la date de décès (quelle qu'en soit la cause). Les patients vivants et sans progression seront censurés à la date de dernières nouvelles. Un minimum d'un an pour le dernier patient inclus est nécessaire.

4.4.5.2 Evaluation de la survie sans progression

L'échelle de temps considérée sera le mois.

La survie sans progression sera représentée graphiquement grâce à l'estimateur de Kaplan Meier et les taux de survie à différentes temporalités (6, 9, 12 et 18 mois) seront calculés ainsi que leurs intervalles de confiance à 95 %.

4.4.6 Time to autonomy deterioration

The analysis will be done if we have the questionnaire at baseline and at least one follow-up for the majority of patients.

4.4.6.1 Definition

It is defined as the time between the date of inclusion and the date on which the IADL score decreased by at least one point from the score at inclusion. Patients alive or deceased without deterioration of autonomy will be censored at the date of last IADL assessment or the date of death.

4.4.6.2 Evaluation

The time scale considered will be the month.

The time to degradation of autonomy will be plotted using the Kaplan Meier estimator and the 6, 9, 12, 18 month rates will be calculated along with their 95% confidence intervals.

4.4.7 Time to QOL deterioration

The analysis will be done if we have the questionnaire at baseline and at least one follow-up for the majority of patients.

4.4.7.1 Definition

It is defined as the time between the date of inclusion and the date of deterioration of the Spitzer QoL Index by 2 points from the score at inclusion. Patients alive or deceased without deterioration will be censored at the date of last QoL assessment or the date of death.

4.4.7.2 Evaluation

The time scale considered will be the month.

The time to deterioration of quality of life will be plotted using the Kaplan Meier estimator, and the 6-, 9-, 12-, and 18-month rates will be calculated along with their 95% confidence intervals.

4.5 Safety

Population : ITTm

Safety will be evaluated by:

- Duration of treatment, doses received, dose reductions, and deferrals;
- Toxicities described according to NCI-CTC version 4.0 criteria;
- Number and description of SAEs

4.5.1 Regorafnib

4.5.1.1 Treatment duration

Treatment duration will be described by:

- The number of cycles per patient;
- The duration of treatment (converted into months) will be calculated by the formula

  Date last tablet taken - date first tablet taken + 1d
- The therapeutic breaks and the days without taking tablets during this period will not be subtracted from this duration.

It will be described according to the usual descriptive statistics.

4.5.1.2 Doses

Compliance will be calculated according to the formula:

(Cumulative dose received (in mg) / theoretical protocol dose (in mg)) x 100

The protocol treatment dose is 4 tablets of 40 mg per day, i.e. 160 mg per day (21 days of treatment and 7 days without treatment, i.e. cycles of 28 days).

Compliance will be described according to the usual descriptive statistics.

4.5.1.3 Postponement of cures, modification of administration and reason

- The number and percentage of patients with at least one deferral of treatment and the reasons for these deferrals
- The number of patients who had at least one dose change will be described. The causes of dose modifications will be presented. A listing of others will be provided.
- The number and percentage of patients who have permanently stopped the protocol treatment and the reasons for stopping treatment will be described.

All parameters will be described according to standard descriptive statistics.

4.5.1.4 Subsequent lines

- The number of patients who received a subsequent line and subsequent patterns will be described.
- The number of patients who had resection of the primary and metastases and the outcome of the resection will be described.

All parameters will be described according to standard descriptive statistics.

4.5.2 Toxicities

On-treatment toxicities will be described according to NCI-CTC version 4.0 criteria by:

- The number and percentage of patients who experienced at least one toxicity over all courses of treatment by grade;
- The number and percentage of patients who experienced at least one maximum grade 3-4-5 toxicity over all courses or at least one maximum grade 1-2 toxicity;
- Toxicities will be described according to causality to treatment and by SOC (by preferred term).
- The number of toxicities that resulted in an SAE

4.5.3 SAEs

A summary of the SAEs will be provided by pharmacovigilance.

4.6 Exploratory analyses

4.6.1 Definition

The exploratory analysis will investigate the predictive factors for response, overall survival, and progression-free survival with regorafenib therapy.

Prior to any inferential analysis, descriptive statistics of the predictive factors will be performed to assess the feasibility of this analysis.

The variables for which the p-value is lower than 0.20 in univariate analysis or judged clinically relevant among the list to be defined will be retained for the multivariate analysis. The prognostic factors studied will be the geriatric parameters.

4.6.2 Evaluation

For univariate and multivariate analyses, hazard ratios will be estimated using a Cox model (Cox, 1984). The proportionality of the rates will be tested using the graphical representation and the test based on Schöenfeld's residuals (Grambsch, 1994); the linearity of the effect of the continuous variables on the risk will be assessed from the graphical representation of the martingale residuals. Confidence intervals for the coefficient estimates of the Cox models will be calculated using the Wald method.

Several multivariate models can be constructed. The comparison of the different models obtained will be carried out according to a measure of adequacy of the model (AIC), a measure of calibration (O'Quigley's R^2) and a measure of accuracy (Breier score).

In an exploratory way, in order to study the temporal evolution of geriatric and quality of life scores (Spitzer QoL Index, IADL, ...), mixed models of analysis of variance for repeated measures of each of the scores will be carried out.