FFCD 1404 - REGOLD

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

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COORDINATOR

Pr Thomas APARICIO
Department of Gastroenterology and Digestive Oncology
Avicenne Hospital
125 rue de Stalingrad - 93009 BOBIGNY cedex
Tel : 01 48 95 54 31 Fax : 01 48 95 54 39
email: thomas.aparicio@avc.aphp.fr

CO-SCIENTIFIC MANAGER

Dr Gaëtan DES GUETZ
Medical Oncology Department
Avicenne Hospital
125 rue de Stalingrad - 93009 BOBIGNY cedex
Tel : 01 48 95 50 31 Fax : 01 48 95 50 35
email: gaetan.des-guetz@avc.aphp.fr

PROTOCOL **DRAFTING COMMITTEE**
T. APARICIO, G. DES GUETZ, M HEBBAR, T LANDRE, K LE MALICOT, M SCHNEIDER , F PAMOUKDJIAN, J TAIEB, D TOUGERON

PROMOTER:
Fédération Francophone de Cancérologie Digestive (FFCD) - 7 Bd Jeanne d'Arc - BP87900 - 21079 Dijon Cedex

CENTER FOR RANDOMIZATION-MANAGEMENT-ANALYSIS (CRGA)
Fédération Francophone de Cancérologie Digestive (FFCD) : Faculté de Médecine, 7 Boulevard Jeanne d'Arc, BP 87900, 21079 Dijon Cedex, France

Administrative Director : **Cécile GIRAULT**

Tel: + 33 (0)3 80 66 80 13 - Fax: + 33 (0)3 80 38 18 41
E-mail : cgirault@u-bourgogne.fr

Statistician: **Carole MONTERYMARD**

Tel: + 33 (0)3 80 39 34 84 - Fax: + 33 (0)3 80 38 18 41
E-mail: carole.monterymard@u-bourgogne.fr

Project Manager: **Martina SCHNEIDER**

Tel: + 33 (0)3 80 39 34 83 - Fax: + 33 (0)3 80 38 18 41
E-mail : martina.schneider@u-bourgogne.fr

SUMMARY

LIST OF ABBREVIATIONS

ACE	Carcinoembryonic antigen
DNA	Deoxyribonucleic acid
ALAT	Alanine aminotransferase (or SGPT: serum glutamic pyruvic transaminase)
ASAT	Aspartate-aminotransferase (or SGOT: serum glutamic oxaloacetic transaminase)
BPC	Good Clinical Practice
JRC	Colorectal carcinoma
CCRm	Metastatic colorectal carcinoma
CIRD	Independent Data Review Committee
CO	Observation booklet
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EI	Adverse event
ISG	Serious adverse event
FFCD	French-speaking Federation of Digestive Oncology
HR	Hazard ratio
IC	Confidence interval
MRI	Magnetic resonance imaging
ITT	Intent To Treat
NCI-CTCAE	National Cancer Institute - Common Toxicity Criteria for Adverse Events
p.o.	Per os
PAL	Alkaline phosphatases
QDV	Quality of life
RECIST	Criteria for assessing tumor response in solid tumors
SG	Overall survival
CT	CT scan
PA	Blood Pressure
VKAS	Anti-vitamin K
NFS	Blood Count
GGT	Gamma GT
ARC	Clinical Research Associate
INR	International Normalized Ratio
CPR	Summary of product features

EXAMINATION AND FOLLOW-UP SCHEDULE

	Before inclusion			During treatment (until progression)					After treatment
	J -21	J -14	J -7	C1 : D1, D7 and D14 C2 : D1, D7 and D14	D1 of each cycle (every 4 weeks)	D14 of each cycle	Every 8 weeks after the start of treatment	End of treatment visit	Every 8 weeks
Informed consent	X								
Clinical examination		X		X	X		X	X	X
Weight, height, BP		X		X	X		X	X	
ECOG		X			X		X	X	X
Geriatric questionnaires, quality of life		X			X		X		
Biological check-up 1[1]			X		X		X		
Biological check-up 2[1]						X		X	
Urine dipstick ± 24h proteinuria		X			X		X		
ECG		X			X[2]				
Thoracic and abdominal-pelvic CT	X						X		
ACE			X		X		X		
Cardiac ultrasound or myocardial scintigraphy ± cardiological opinion in case of cardiopathy[3]	X								
Assessment of treatment toxicity				X	X		X	X	

Biological check-up 1: CBC-PQ, natraemia, kalemia, calcemia, magnesemia, phosphoremia, uricemia, creatininemia, albuminemia, ASAT, ALAT, PAL, total and conjugated bilirubinemia, GGT, TP, TSH, lipase, INR for patients treated with AVK.
Biological check-up 2: CBC-Pq, natraemia, kalemia, creatinine, creatinine clearance, ASAT, ALAT, PAL, total and conjugated bilirubin, GGT INR for patients treated with AVK.

[1] For patients treated with an anti-coagulant, a coagulation test should be performed, if the values are outside the therapeutic range the dose of anticoagulant should be modified and a coagulation check should be done every week until stabilization.

[2] During treatment, an ECG will be done according to the investigator's choice.

[3] In case of heart disease, cardiac echography or myocardial scintigraphy, completed by a cardiologist's opinion if necessary, **dated less than 3 months before inclusion.**

1. BACKGROUND INFORMATION AND RATIONALE FOR THE STUDY

1.1 General

In France, the incidence of colorectal cancer (CRC) continues to increase. Approximately 50% of CRCs occur in patients over the age of 70. Cancers in general are the second most common cause of death in patients over 70 years old.
With the aging of the population expected in the coming years, the proportion of patients over 70 years of age will increase further. On the other hand, life expectancy is increasing among elderly patients. It reaches 12 years for patients over 75 years old and more than 8 years for those over 80 years old. The discussion of a CRC in a patient over 70 years of age in a multidisciplinary consultation meeting is therefore frequent and the course of action is often difficult to determine because of the lack of consensus data specific to elderly patients.
Elderly people are a heterogeneous population. Some people age well, have few chronic pathologies and remain independent. But many suffer from several organ pathologies, malnutrition, functional walking disorders, sensory deficits, but also cognitive or psychological disorders such as depression (linked to bereavement, disabilities...). Polymedication, as a consequence of comorbidities, is therefore frequent with a risk of iatrogeny increased by the side effects of the drugs and their interactions. All these elements, in close interaction with social and economic conditions, determine the health status of elderly subjects. The presence of co-morbidities reduces life expectancy and may in itself be a contraindication to treatment (2). There is also a risk of decompensation of comorbidities in the presence of a new pathology or its treatment.
The question of adapting treatment to the patient takes on its full meaning in oncogeriatrics; treatment must necessarily be personalized. The recent recommendations of the INCa propose a geriatric evaluation of elderly patients undergoing cancer treatment. When carried out, it will modify the therapeutic management of approximately 20% of patients, particularly in the case of loss of autonomy or malnutrition (3).
Assessment of geriatric parameters may allow treatment to be tailored. In the FFCD 2001-02 study, which compared 5-fluorouracil monotherapy with FOLFIRI in first-line metastatic colorectal cancer in patients over 75 years of age, loss of autonomy and cognitive impairment were associated with the occurrence of toxicity (4). Recently, a screening tool has been proposed to select patients for geriatric evaluation (5).

1.2 Treatment of metastatic colorectal cancer with regorafenib

Regorafenib is an oral multitargeted inhibitor with initial hepatic metabolism, targeting both the tumor and its vasculature. Regorafenib inhibits VEGFR-2 and -3, and kinases located in tumor cells (RET, KIT, PDGFR, and Raf). In preclinical studies, regorafenib has shown antitumor activity in a broad spectrum of animal tumor models including CRC. In a Phase Ib study, regorafenib showed an acceptable toxicity profile and initial evidence of antitumor efficacy in patients with metastatic CRC (6). In a Phase III study (CORRECT), regorafenib treatment significantly increased overall survival in patients with metastatic CRC who had received all previously approved therapies (1). Other efficacy parameters such as progression-free survival (PFS) and tumor control rate were also improved.

Subgroup analyses, including patients over 65 years of age, showed an improvement in these parameters compared to placebo.
A retrospective analysis specifically studied the impact of regorafenib treatment in patients over 65 years of age compared with younger patients (7). The hazard ratio for overall survival (regorafenib/placebo) was 0.72 (95% CI 0.56-0.91) in patients younger than 65 years and 0.86 (95% CI 0.61-1.19) in patients older than 65 years (interaction test p = 0.405). Treatment exposure was similar in both groups (<65 years *vs.* >65 years) with respect to median treatment duration (7.6 weeks *vs.* 7.1 weeks), median daily dose (160 mg in each group), and median proportion of planned dose taken of regorafenib (83.3% *vs.* 78.6%). Most patients had treatment-related side effects (<65 years: 93.8%; ≥65 years: 91.7%). The rate of regorafenib-related grade ≥3 adverse events was 52% in patients <65 years, 57% in patients between 65 and 74 years, and 66% in patients >75 years. In the latter group, hypertension was more common than in younger patients.
Although data on the use of targeted therapies in metastatic CRC are limited in elderly patients, a phase III study specific to elderly patients showed that bevacizumab prolonged progression-free survival (8). A randomized phase II study of the FFCD (PRODIGE 20), the results of which are currently being analyzed, is designed to evaluate the safety and evolution of geriatric parameters during treatment with bevacizumab.
The objective of the REGOLD study is to better describe the effects of regorafenib in elderly patients with metastatic CRC. In addition to safety and efficacy endpoints, quality of life and geriatric parameters will be assessed.

2. OBJECTIVES OF THE STUDY

2.1 Main objective

Assessment of tumor control rate (defined as the number of patients not progressing i.e. with complete tumor response, partial tumor response or tumor stability) on regorafenib therapy, 2 months after initiation of therapy, in elderly patients with metastatic colorectal cancer (mCRC) who have been previously treated with available therapies.

2.2 Secondary Objectives

Evaluate:
- Overall survival at 1 year
- Progression-free survival at 1 year
- Tumor control rate at 2 months (centralized review)
- Objective response rate assessed from the best response under treatment
- Time to therapeutic failure
- Time to degradation of autonomy
- Time to degradation of quality of life
- Geriatric prognostic and predictive parameters
- Dose-intensity and its correlation with tumor control rate
- Tolerance of regorafenib according to the NCI-CTC AE version 4.0 scale

3. PATIENT SELECTION

3.1 Inclusion criteria

- Metastatic colorectal cancer with histological evidence
- Measurable disease according to RECIST 1.1 criteria
- Age ≥ 70 years
- ECOG ≤ 1
- Life expectancy greater than or equal to 3 months
- Biological workup: hemoglobin ≥ 9 g/dL, PNN ≥ 1500/mm3, platelets ≥ 100,000/mm3, bilirubin ≤ 1.5N, AST, ALT and PAL ≤ 2.5N (≤ 5N if liver metastases), lipase ≤1.5N, PT≥ 70%, creatinine clearance ≥ 30 mL/min
- Patients who have failed fluoropyrimidine-based chemotherapy, anti-VEGF therapy, and anti-EGFR therapy (if the cancer expresses the non-mutated RAS gene), who have progressed on this therapy, or patients who have discontinued this therapy for unacceptable toxicity
- Completed geriatric patient and team questionnaires
- Signed informed consent

3.2 Criteria for non-inclusion

- Inability to swallow tablets (crushed tablets are not allowed)
- **Previous treatment with regorafenib or another multikinase inhibitor**
- Other cancer within 5 years prior to inclusion, except cervical cancer *in situ*, non-melanoma skin cancer and superficial bladder cancer treated curatively
- Radiation therapy: - with extended fields, within 4 weeks, - with limited fields, within 2 weeks, prior to inclusion. The site treated in this way must have demonstrated progression, if it is the only evaluable site
- Unresolved > grade 1 toxicity attributed to prior therapy
- Major surgery within 28 days of starting treatment
- Unhealed wound, ulcer or bone fracture
- Congestive heart failure of class >2 according to the NYHA classification
- Unstable angina or angina that started less than 3 months ago
- Myocardial infarction less than 6 months before the start of treatment
- Uncontrolled hypertension (systolic pressure > 150 mm Hg or diastolic pressure > 90 mm Hg despite optimal treatment)
- Pheochromocytoma
- Arterial or venous thromboembolic event within 6 months prior to the start of treatment
- Clinically active infection of grade >2
- HIV infection
- Chronic viral hepatitis B or C requiring antiviral treatment
- Cirrhosis
- Known or suspected brain metastasis
- Bleeding grade >3 within 4 weeks of starting treatment
- Symptomatic pulmonary fibrosis
- Proteinuria > grade 3
- Malabsorption
- Known hypersensitivity to the study drug or to a drug of the same class or to an excipient
- Systemic anti-cancer treatment during the study or within 4 weeks prior to initiation of treatment
- Concomitant treatment with a CYP3A4 inhibitor or inducer or a UGT1A9 inhibitor
- Social, psychological or medical condition that may interfere with participation in the study or its evaluation

4. INCLUSION ASSESSMENT

- Within 3 months prior to inclusion:
In case of a history of heart disease, it is recommended to have the results of a cardiac echography or a myocardial scan, completed by a cardiologist's opinion if necessary.

- Within 21 days prior to inclusion:
Thoracoabdomino-pelvic CT or hepatic MRI + non-injected thoracic CT scan if contraindication to iodinated contrast injection.

- Within 14 days prior to inclusion:
- medical history, clinical examination (weight, height, BP, ECOG status)
- completion of the "patient self-questionnaire at inclusion" (Appendix 2)
- Completion of the "Inclusion Team Questionnaire" (Appendix 3)
- Urine dipstick, if protein > +, then do the 24h proteinuria
- ECG

- Within 7 days prior to inclusion:
- biological assessment including:
    - NFS-Plates
    - natremia, kalemia
    - calcemia, magnesemia, phosphoremia, uricemia
    - creatinine clearance (Cockcroft and Gault) (Appendix 5)
    - creatinine, albumin
    - liver check-up: ASAT, ALAT, PAL, total and conjugated bilirubin, GGT
    - TP
    - ACE
    - TSH
    - Lipase
    - INR for patients treated with VKAs

5. INCLUSION

Inclusion will be done after a complete eligibility check-up and the signature of the informed consent. Inclusion will be carried out by the CRGA of the FFCD after reception of the fax of inclusion (form 1 of the observation booklet) at 03 80 38 18 41. The CRGA is open from Monday to Friday from 9 am to 6 pm.
A confirmation of inclusion will be faxed back to the investigator.
After the patient is enrolled in the study, treatment should be started within 7 days.
An observation booklet will be sent at the opening of the center. A new observation book will be sent after each inclusion.

6. DIAGRAM OF THE STUDY

This is a single-arm Phase II study. All patients included, after verification of the inclusion criteria, will be treated according to the same regimen. Each cycle lasts 28 days (21 days of treatment and 7 days without treatment).

7. TREATMENT

Regorafenib is not provided as it is in its indication.
The initial dose will be 160 mg (4 tablets) taken orally once daily for 21 days, followed by 7 days without treatment.
They should be taken at a fixed time and in one go at the end of a light meal in a large glass of water.
Forgotten or vomited tablets should not be taken again.
Dose modifications will be made according to the protocol in 40 mg steps. The minimum recommended dose is 80 mg.
Reasons for dose reduction or discontinuation of treatment will be collected in the observation booklet.
Compliance with the treatment will be evaluated for each cycle by the investigator, using the compliance booklet given to the patient at the beginning of the treatment and reported at each consultation. This compliance will be reported in the observation booklet.

7.1 Duration of treatment

Causes of discontinuation are:
- progress
- occurrence of a second cancer
- Dose reduction of more than 2 times 40 mg
- interruption of treatment for more than 4 consecutive weeks
- patient refusal
- withdrawal of consent
- continuation of the study deleterious to the patient according to the investigator

Patients who discontinue study treatment will be managed according to local guidelines. The administration of any other anti-cancer treatment will be collected in the observation booklet at a follow-up visit.
Patients will be followed every 2 months after discontinuation of treatment, regardless of the reason for discontinuation, until death except for patients who have withdrawn their consent.
Patients who stopped treatment before progression will be followed to assess the date of first progression.

7.2 Dose adjustment

Toxicities will be evaluated by questioning and clinical examination at D1, D7, and D14 of the 1st cycle and of the 2^{e} cycle then at D1 of each following cycle. They will be evaluated by biology at D14 and D28 of each cycle. They will be graded according to the NCI-CTC AE version 4.0 criteria (Appendix 7).
The decision to reduce the dose is based on toxicity throughout the cycle.
The doses will be adapted according to the RCP (see table below).

Discontinuation of treatment and/or reduction in dosage may be necessary depending on tolerance. Dosage changes should be made in 40 mg (one tablet) increments. The minimum recommended daily dose is 80 mg. The dose may be increased if there is complete recovery of the side effect after dose reduction. The maximum daily dose is 160 mg.

A) Dosage modifications and recommended actions for hand-foot syndrome (MPS/palmoplantar erythrodysesthesia):

Grade of skin toxicity	Occurrence	Dosage changes and recommended actions
Grade 1	All cases	Maintain dosage and institute symptomatic treatment immediately.
Grade 2	1re occurred	Reduce the dose by 40 mg (one tablet) and start symptomatic treatment immediately.
	No improvement within 7 days or 2e occurred	Interrupt treatment until toxicity disappears or decreases to a grade ≤ 1. When treatment is resumed, reduce the dose by 40 mg (one tablet).
	3e occurred	Immediately initiate symptomatic treatment. Interrupt treatment until toxicity has resolved or decreased to a grade ≤ 1. When treatment is resumed, reduce the dose by 40 mg (one tablet) if it had been increased after previous episodes.
	4e occurred	Stop the treatment permanently.
Grade 3	1re occurred	Immediately institute symptomatic treatment. Interrupt treatment for a minimum of 7 days until toxicity disappears or decreases to a grade ≤ 1. When treatment is resumed, reduce the dose by 40 mg (one tablet).
	2e occurred	Immediately institute symptomatic treatment. Interrupt treatment for a minimum of 7 days until toxicity disappears or decreases to a grade ≤ 1. When treatment is resumed, reduce the dose by 40 mg (one tablet).
	3e occurred	Stop the treatment permanently.

Treatment should be permanently discontinued in case of intolerance to the 80 mg daily dose.

B) Dosage modifications and recommended actions for drug-related liver function abnormalities

Elevated ALT and/or AST levels	Occurrence	Dosage changes and recommended actions
<= 5 times the upper limit of normal (ULN) (Grade 2 maximum)	All cases	Continue regorafenib therapy. Monitor liver function weekly until transaminases return to <3 times ULN (grade 1) or to baseline.
> 5 times ULN (Grade 3) ≤ 20 times ULN	1re occurred	Discontinue regorafenib. Monitor transaminases weekly until they return to < 3 times ULN or to baseline.
		Resumption of treatment: reinstate regorafenib, reduce dose by 40 mg (one tablet) if potential benefit outweighs risk of hepatotoxicity. Monitor liver function weekly for at least 4 weeks.
	New occurrence	**Permanent discontinuation** of regorafenib.
> 20 times ULN (Grade 4)	All cases	**Permanent discontinuation** of regorafenib.

Elevated ALT and/or AST levels	Occurrence	Dosage changes and recommended actions
> 3 times ULN (Grade 2 or higher) **with concomitant elevation of bilirubin > 2 times ULN**	All cases	**Permanent discontinuation** of regorafenib. Monitor liver function weekly until normalization or return to baseline. Exception: Patients with Gilbert's syndrome who develop elevated transaminases should be managed as described above for corresponding elevations in ALT and/or AST.

7.3 Contraindicated treatments

Regorafenib is metabolized by cytochrome CYP3A4 and uridine diphosphate glucuronosyl transferase UGT1A9.
Coadministration of regorafenib with potent CYP3A4 inhibitors (such as clarithromycin, grapefruit juice, itraconazole, ketoconazole, posaconazole, telithromycin and voriconazole) should be avoided.
Coadministration of regorafenib with strong inducers of CYP3A4 (such as rifampin, phenytoin, carbamazepine, phenobarbital, or St. John's Wort) should be avoided.

8. PATIENT MONITORING

8.1 during treatment :

- Clinical examination: weight, height, BP, collection of toxicities and clinical tumor assessment
    - Cycle 1 and 2: at D1, D7 and D14
    - Cycles 3 and following: at D1 of each cycle
    - At the end of treatment visit

The ECOG is completed on Day 1 of each cycle (cycle 1 and following) and at the end-of-treatment visit.

- Bioassay:

At each cycle: at D1 and D14; (for cycle 1, the biological test at D1 can be the inclusion test, if it is less than 14 days old).

The assessment at Day 1: CBC-platelets, natraemia, kalemia, calcemia, magnesemia, phosphoremia, uricemia, creatininemia, creatinine clearance, albuminemia, ASAT, ALAT, PAL, total and conjugated bilirubinemia, GGT, TP, TSH, lipase, INR for patients treated with AVK.

Assessment at D14: CBC/blood platelets, creatinine clearance, natraemia, kalemia, creatinine, ASAT, ALAT, PAL, total and conjugated bilirubin, GGT, INR for patients treated with AVK.

- At the end-of-treatment visit: CBC/blood platelet count, natraemia, kalemia, creatinine, creatinine clearance, AST, ALT, PAL, total and conjugated bilirubin, GGT

A coagulation test should be performed at D1 and D14 of each cycle, if patients are treated with anticoagulant. If the values are outside the therapeutic range, the dose of anticoagulant should be modified and a coagulation test should be performed every week until stabilization.

- Other follow-up:

During treatment, an ECG will be performed if deemed useful by the investigator.

Every 4 weeks, until progression, CEA measurement will be performed as well as quality of life and geriatric parameters assessment.
Every 8 weeks, until progression, a thoraco-abdomino-pelvic scan will be performed to evaluate the tumor response.

8.2 After treatment :

- If treatment is stopped for progression: the patient will be followed up approximately every 8 weeks to collect survival data and subsequent anti-cancer treatments.
- if the treatment is stopped for another reason: the patient will be followed every 8 weeks with a thoraco-abdomino-pelvic scanner, until progression. Then he will be followed approximately every 8 weeks to collect survival data and subsequent anti-cancer treatments.

9. CENTRALIZED REVIEW AND ANCILLARY STUDY

Radiological responses will be evaluated according to RECIST version 1.1 criteria (Appendix 4) and will be reviewed by a panel of independent radiologists.
Remember to keep the CDs and the CT scan report in the patient's file; the CRA FFCD will make a copy of these imaging studies for centralization at the AMRC.
In addition, ancillary imaging studies will also be performed on these copies.

10. MANAGEMENT OF SERIOUS ADVERSE EVENTS (SIA)

10.1 Security assessment parameters

Safety will be assessed by evaluating the general and clinical condition of the patients and by collecting events occurring between visits during consultations, and by regular blood tests. Toxicities will be assessed using the NCI-CTCAE Toxicity Scale version 4.0 (Appendix 7).
In case of an emergency, the patient, his family or his physician should call the investigator to inform him of an event.

10.2 Definitions

a. Adverse Event (AE)
An adverse event is a harmful occurrence in a person who is a subject of biomedical research, whether or not the occurrence is related to the research or the product being investigated.
All adverse events will be recorded in the observation book on the pages provided for this purpose according to their grade.

b. Serious Adverse Event (SAE)
A serious adverse event is any event that
- Resulting in death
- Life-threatening
- Resulting in hospitalization or prolonged hospitalization
- Causing permanent disability or severe temporary incapacity
- Causing a birth defect, fetal malformation or abortion

- Medically significant (examples: overdoses, second cancers, and new developments may be considered medically significant).

The terms disability and incapacity correspond to any temporary or permanent physical or psychological handicap, clinically significant and affecting the physical activity and/or quality of life of the patient.
Any clinical event or laboratory result considered serious by the investigator and not corresponding to the severity criteria defined above is considered medically significant. They may put the patient at risk and require medical intervention to prevent an outcome corresponding to one of the severity criteria mentioned above (examples: overdose, second cancers, pregnancies and new facts may be considered medically significant).

c. Undesirable Effect
Any noxious and unintended response to an investigational drug at any dose or to any investigational component. An adverse reaction is serious if it meets a severity criterion.

d. Unexpected Serious Adverse Effect
An unexpected serious adverse reaction is an event that is not mentioned, or that differs in nature, intensity, or evolution from the product reference document (or RCPs).

e. New fact
A new fact can be: an unexpected frequency of an expected SAE, an SAE related to the trial procedure.
f. Intensity (or severity)
The intensity criterion should not be confused with the severity criterion, which is used as a guide to define reporting obligations.
The intensity of the events will be estimated according to the extract of the NCI CTC-AE classification version 4.0 (Appendix 7). The intensity of adverse events not listed in this classification will be assessed according to the following qualifiers:
- Mild (grade 1): does not affect the patient's usual daily activity
- Moderate (grade 2): disrupts the patient's usual daily activity
- Severe (grade 3): prevents the patient's usual daily activity
- Very severe (grade 4): requires resuscitative measures / life threatening
- Death (grade 5)

g. Causal relationship
- Related: an event is said to be related when a causal relationship between the event and the product under study can reasonably be suspected
- Unrelated: an event is said to be unrelated when a causal relationship between the event and the product under study cannot reasonably be suspected
- Doubtful: causality is said to be "doubtful" when there is doubt about the causal relationship between the event and the product under study (the relationship can then be neither formally excluded nor formally affirmed)

10.3 Reference documents for the study

The reference document for assessing the expected or unexpected nature of the SAEs will be, for regorafenib, the Summary of Product Characteristics for STIVARGA® 40 mg (Appendix 8).
The version of the PCRs used for the definition of expected/unexpected will be the latest available on the anniversary date of the start of the trial.

10.4 Events of particular interest, to be declared as a SAE

Within the framework of this protocol, we ask you to report on the SAE form, even if none of the classic severity criteria are met:
- Grade 3-4 liver function tests
- hepatic insufficiency

10.5 Events not to be considered serious

Disease progression should not be considered an SAE.
Events that are potentially related to progression but may also be secondary to treatment will continue to be reported (e.g. thromboembolic events, bleeding phenomena, perforations).
Due to the severity of the disease in this study, certain conditions defined as an SAE will be excluded from the SAE reporting procedure, namely:
- Hospitalization or surgery specifically related to the treatment of the disease
- Hospitalization performed to simplify study treatments or procedures.

10.6 Conduct

The investigator informs the sponsor of all Serious Adverse Events (expected and unexpected), whether or not attributable to the research, that occur during the study or within 30 days of the last treatment administration.
The investigator informs the sponsor of all Adverse Events of Special Interest (even "non-serious" ones) that occur during the study or within 30 days of the last treatment administration.

All Delayed Serious Adverse Events (occurring after this 30-day period) considered reasonably related to the protocol treatment(s) or research should be reported without time limitation.

The report is made by faxing the "notification of a serious adverse event" form (Appendix 9), documented as precisely as possible, dated and signed, within 24 working hours of their knowledge to the **FFCD's Randomization Management Analysis Center (CRGA) by fax to 03 80 38 18 41.**

The investigator is responsible for appropriate medical follow-up of patients until resolution or stabilization of the effect or until the patient's death. This may sometimes involve extending follow-up after the trial patient's protocol treatment has been discontinued.
It transmits the additional information to the sponsor using an SAE reporting form (checking the "Follow-up" box and incrementing the number, to specify that it is a follow-up report and not an initial report) within 24 hours of obtaining it. It also forwards the last follow-up to the resolution or stabilization of the SAE.
It responds to requests for additional information to document the initial observation.

The sponsor is responsible, upon receipt of the investigator's report of the serious adverse event, for issuing an opinion on the causal relationship between the serious adverse event and the study product(s).

If the serious adverse event is linked by the investigator and/or sponsor to one of the study products (i.e., it is a serious adverse event), the investigator and/or sponsor must establish the expected or unexpected nature of this event.
In the case of an unexpected serious adverse reaction, or if it is a new event, the sponsor prepares an initial report which will be sent to the ANSM, the CPP and the EMA (via EudraVigilance) within 7 days in the case of death or life-threatening situation, otherwise within 15 days.
If it is an expected serious adverse event, it will be collected for the semi-annual and annual safety reports.

11. STATISTICAL ANALYSIS

11.1 Judging criteria

1) Primary endpoint

Tumor control rate is defined as the percentage of patients with complete tumor response, partial tumor response, or tumor stability on regorafenib therapy at 2 months after initiation of therapy as determined by the investigator (RECIST V1.1 criteria)

2) Secondary criteria

The **secondary endpoints** are defined as follows:

- Overall treatment **tolerance** will be assessed by the rate of observed toxicities, graded according to NCI-CTC v4.

- Overall survival is defined as the time from the date of inclusion to the date of death from any cause. Patients lost to follow-up or alive at the time of analysis will be censored at the date of last report. A minimum follow-up of 1 year for the last included patient is required.

- The tumor control rate assessed in centralized review is defined as the percentage of patients with complete tumor response, partial tumor response, or tumor stability on regorafenib therapy 2 months after the start of therapy (RECIST criteria V1.1).

- The objective response rate is defined as the occurrence of at least one complete or partial response assessed from the best response (according to RECIST v1.1 criteria) during the treatment evaluations (Appendix 4). Patients who discontinue the study without response assessment will be considered non-responders.

- Time to treatment failure is defined as the time from the date of inclusion to the date of treatment discontinuation (regardless of cause) or death (regardless of cause). Living patients without treatment discontinuation will be censored at the date of last treatment administration.

- Progression-free survival is defined as the time from the date of inclusion to the date of first investigator-rated progression (clinical or radiological) or death (from any cause). Patients alive without progression will be censored at the date of last news. A minimum

follow-up of 1 year for the last included patient is required.

- The regorafenib dose intensity will be calculated during the first 2 cycles of treatment **and over the** entire treatment period. The theoretical dose intensity (TDI) (mg/cycle) is 3360 mg ((160mg/d x 21d). The dose intensity (DI) actually received is equal to the total dose received divided by the total duration of treatment. The relative dose intensity (DIR) is equal to DI / DIT.

- Time to deterioration in independence is defined as the time from the date of inclusion to the date on which the IADL score (Appendix 2) has decreased by at least 1 point from the score calculated 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.

- Time to deterioration in quality of life is defined as the time from the date of inclusion to the date of deterioration of the Spitzer QoL Index (9) (Appendix 3) 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.

11.2 Exploratory evaluation of geriatric parameters

It is recommended that each patient has had a geriatric consultation prior to inclusion.

An exploratory analysis is planned to look for geriatric prognostic factors for the primary endpoint. An analysis of the evolution of geriatric parameters during the follow-up will also be performed.

The "patient" self-questionnaire including the collection of activity of daily living and the "team" questionnaire including the quality of life (Spitzer QoL Index) will be completed at inclusion and at each evaluation (every 4 weeks).

The self-questionnaire will be completed by the patient. The "team" questionnaire will be completed by a clinical research associate, a nurse or the investigator depending on the organization of the service.

The 2 questionnaires include the assessment of geriatric parameters with the following domains: functional status, mobility, cognition, depression, energy, social context and quality of life; physical activity, nutrition, hearing and vision will only be completed at inclusion. A cut-off value is determined for each domain.

The questionnaires and self-questionnaires are presented in Appendices 2 and 3. These evaluation questionnaires have been used in onco-geriatrics, particularly as self-questionnaires (10-14).

The geriatric parameters are:

1) Co-morbidity (Self questionnaire and Team)

To assess the co-morbidity of each patient, the following items will be documented:

- Existence of one or more hospitalizations in the last 12 months for a reason other than cancer management.
- Updated Charlson score (15)

2) Functional status

a) Activities of daily living **(Self questionnaire)**

The self-administered questionnaire replicating the items of the Katz index (16) will be used to measure basic activities of daily living (ADL). Thus, the ADL score for each patient can range from 0 (unable to perform any activity) to 6 (able to perform all activities). Disability in a BDA is defined as the need for assistance with at least one activity of daily living.

Threshold value: <6

b) Instrumental activities of daily living (IADL) **(Self questionnaire)**

The self-administered questionnaire reproducing the IADL items will be used to measure instrumental activities of daily living (IADL) (17). Disability in an IADL is defined as the need for assistance to complete at least one IADL. The denominator will be adjusted to account for patients not performing certain activities listed in the IADL.

The threshold value is: <14 when the patient does or did all IADL activities. A score lower than 14/14 is considered pathological (e.g., if the patient needs help with housework and managing money, the score will be 12/14 and therefore pathological). If the patient has never done certain activities, the score is adjusted according to the denominator corresponding to the maximum number of points possible on the activities performed by the patient (e.g.: if the patient has never done housework, the score will be 12/12, and the IADL is considered normal).

c) Eastern Cooperative Oncology Group Functional Index (ECOG-PS) **(Case report***)*

The ECOG is a five-point scale designed to measure the level of interference of symptoms with normal activity and the number of hours awake in bed (18). An ECOG ≥ 2 is considered a decrease in functional status.

Threshold value = ECOG ≥ 2

3) Mobility (Self questionnaire and Team questionnaire)

To assess mobility, the unipodal station test (19) and the number of falls reported in the last 6 months (or last 2 months at follow-up) will be used. The unipodal station test is considered abnormal if the patient is unable to balance on one leg for more than 5 seconds or if the patient has had a fall in the last 6 months.

Threshold value: monopodal support < 5 seconds or fall in the last 6 months (and in the last 2 months for follow-up)

Volunteer centers will also measure the 4-meter walking speed (TM-4) (20). The TM-4 is done over a distance of eight meters including the two meters of acceleration and deceleration. The time is measured for the central 4 meters, to avoid acceleration and deceleration at both ends of the course. Precise instructions will be given to the patient: "walk at your usual pace, at your ease". The test will be repeated twice. A 4 m walking speed test longer than 4 seconds is considered as pathological (21).

4) Nutrition

a) Body Mass Index **(Observation Booklet)**

The body mass index (BMI) will be calculated for each patient as follows: BMI = Weight (Kg)/[Height (m)]^2 . BMI is an index commonly used to classify overweight and obesity in adults. The World Health Organization (1998) classifies normal weight with a BMI of 18.5 to 24.9 kg/m^2 , overweight with a BMI between 25 and 29.9 kg/m^2 , and obese with a BMI>

30 kg/m^2 . A BMI < 18.5 kg/m^2 is considered underweight and indicates severe malnutrition (22). A BMI < 21 already indicates undernutrition (HAS 2007) in the elderly.

Threshold value in geriatrics: BMI < 21 kg/m^2

b) Mini nutritional evaluation **(Team Questionnaire)**

The Mini Nutritional Assessment (MNA-SF) is a 6-item questionnaire to detect malnutrition. These items are already collected in the G8 Mini Assessment. Patients are considered at risk of malnutrition if they have a score ≤ 11 out of a total of 14 (23).

Threshold value: score ≤ 11

The G8 scale used in the ONCODAGE study will be evaluated (5).

c) Evaluation of weight loss by losing 4kg in 1 year **(Self questionnaire)**

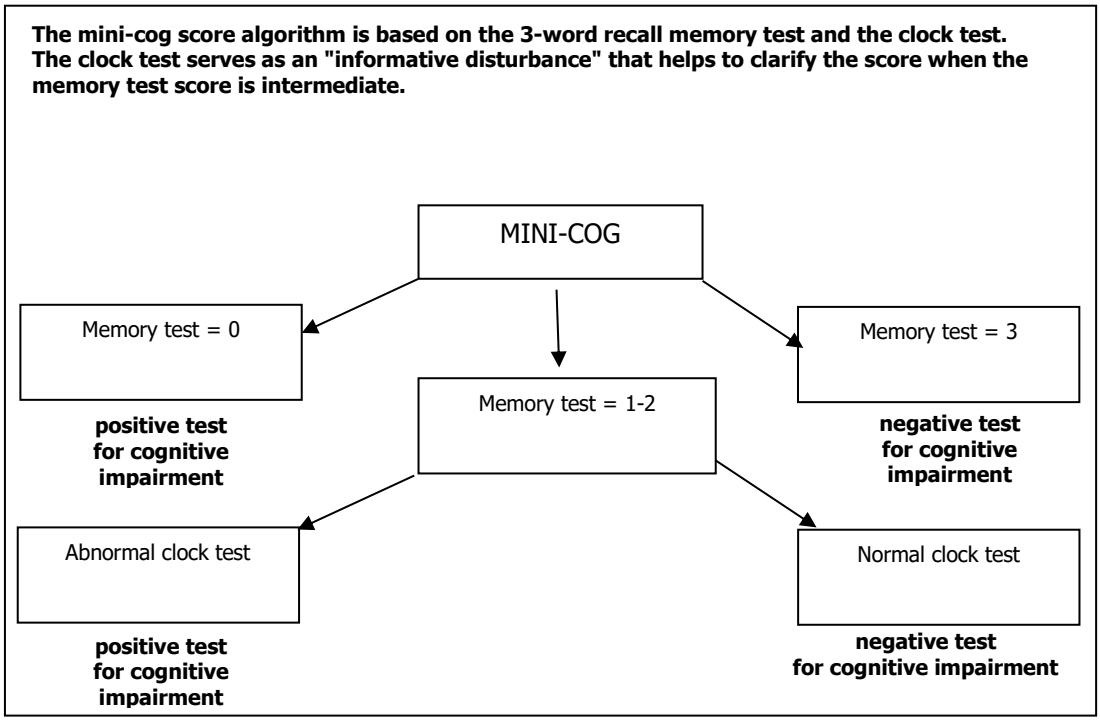
"In the past year, have you involuntarily lost more than 10 pounds?" (20)

5) Cognition (Team Questionnaire)

The Mini-COG will be used to detect cognitive impairment (24).

Scores:

- If 3-word recall = 0 positive test for cognitive impairment
- If the 3 words recall = 1 or 2
  - Either normal clock test: negative test for cognitive impairment
  - Either abnormal clock test: positive test for cognitive impairment
- If recall of 3 words = 3, negative test for cognitive impairment



6) Depression (Self questionnaire)

The 4-item Geriatric Depression Scale (mini GDS) is used to suspect depression. A score of 1 or higher indicates possible depression (25).

Threshold value: ≥ 1

7) Energy (Self questionnaire)

A visual analog scale will be used to assess the energy domain (26). A score < 3 indicates a positive fragility marker for this domain.

Threshold value: < 3

8) Physical activity (Team Questionnaire)

The validated self-questionnaire derived from the Canadian Study of Health and Aging Risk Factor Questionnaire (RFQ) will be used (27). Physical activity will be stratified according to 4 levels of exercise that are scored from 1 to 4 :

4- high level of exercise (more intense than walking at least 3 times a week)

3- moderate exercise (walking 3 times a week)

2- low level of exercise (either walking or more intense than walking, less than 3 times a week or exercise less intense than walking, any frequency)

1- No physical exercise

No exercise or low level of exercise (score 1 or 2) indicates a positive fragility marker for this domain.

Threshold value: ≤ 2

9) Social context (Self questionnaire)

No reference tool yet exists to measure social context in gerontological research. The following question was chosen: *Will you have someone to care for you during the treatment period? If so, who is it?* (Spouse, children, friends, neighbors, caregivers).

Threshold value: no

10) Quality of life (Team Questionnaire)

The Spitzer QoL Index questionnaire will be used to assess quality of life (9).

11) Hearing (Self questionnaire)

The next question will be asked "do you have difficulty hearing or do you have a hearing aid?"

Threshold value: yes

12) Vision (Self questionnaire) (28):

The following questions will be used:

Question 1: "Are you able to read a sentence in the newspaper (with or without glasses)?"

If no to question 1:

Question 2: "Can you read the headlines in the newspaper?

Threshold value: answer no to question 1

11.3 Calculation of the number of subjects required

The clinical assumptions 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 α risk of 5% and 90% power, 42 patients are required.
Patients who discontinue the study prior to 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 show a complete or partial response or stability, then the treatment will be considered not effective.
If 16 or more patients have a complete, partial or stable response, then the treatment is considered effective.

A recruitment of 2 patients per month is planned.

11.4 Statistical analysis

Populations of analysis
All analyses will be done on an intention-to-treat basis on all included patients who have taken at least one treatment tablet.

Descriptive analyses
Continuous variables will be described using mean, standard deviation, median, minimum and maximum, and interquartile range (Q1-Q3).
Qualitative variables will be described using frequencies and percentages. The percentages will be calculated without taking into account the missing modality.

Analysis of the judging criteria
Censored data will be estimated and plotted using the Kaplan Meier (KM) method. Survival times will be described by medians and rates at different time points with their 95% confidence intervals. The median follow-up time will be calculated using the so-called "reverse Kaplan Meier" method.

Tolerance **analysis**
Toxicities will be described, by the number of patients and toxicities according to the different grades and the different SOC. They will also be described by grouping grades 1-2 versus 3-4-5.

Analysis of geriatric parameters
An analysis of prognostic factors for overall survival and progression-free survival will be performed. These analyses will be performed using univariate and multivariate Cox models.
The geriatric parameters and the inclusion variables considered clinically relevant will be studied in univariate. Variables that are significant at the 20% threshold can be introduced into the multivariate models. Several multivariate models can be constructed, and the comparison of the different models obtained will be carried out according to a measure of model adequacy (AIC), a measure of calibration (O'Quigley's R^2) and a measure of accuracy (Breier score).

Exploratory analysis
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 performed.

12. ANCILLARY STUDY

During this study, copies of the evaluation images will be collected for each patient. It is planned to look for predictive markers of response and progression-free survival under regorafenib treatment.

- Fat is now considered as an endocrine and paracrine organ (29). Today we distinguish 2 types of fat, visceral and subcutaneous, because they have a different secretion profile (30). Visceral fat secretes adipokines, some of which are pro-angiogenic and proliferative. Cross-sectional imaging (CT/MRI) is the only technique to separate visceral fat from subcutaneous fat. It has been hypothesized that pro-angiogenic adipokines secreted by visceral fat may influence the response and survival of patients treated with anti-angiogenic drugs. As an exploratory study, a monocentric study of 120 patients treated in 1st line metastatic colorectal cancer was performed: 80 patients were treated with bevacizumab + chemotherapy and 40 patients with chemotherapy alone (31). It is clear that patients treated with bevacizumab with high visceral fat have a poorer 2-month response, shorter progression-free survival and overall survival.

  Other studies of the same type are underway for other cancers and the preliminary results confirm these initial results. The major objective will be to validate that visceral fat area (calculated on the baseline scan) is an independent predictor of response at the first assessment (8-week scan) and of progression-free survival.

- In addition, an exploratory study of tumor density will be conducted based on the analysis of baseline and 8-week scans.
  Three tumor density measurements will be performed for a maximum of 2 targets per organ, on axial slices made after injection of iodinated contrast. For each target, a density measurement by a global region of interest will be performed on the slice showing the largest tumor surface. A density measurement will be performed on the tumor area appearing the most hyperdense. Finally, a measurement will be performed on the most hypodense tumor area. Finally, a density measurement of the underlying healthy organ will also be noted for each scan. The injection time (arterial, portal or late) will be noted for each target, as well as the quantity of contrast medium used (noted on the radiological report). These measurements will be repeated on the 8-week scan.
  The objective will be to determine, with the help of ROC curves, the threshold of variation of the tumor density allowing to predict the response and the progression.

  - Finally, sarcopenia has been shown to be a predictive factor for toxicity of chemotherapy in colorectal cancers (32) and also of sorafenib (another tyrosine kinase inhibitor close to regorafenib) in hepatocellular carcinoma (33). Sarcopenia will be analyzed on abdominal sections to investigate its predictive value of toxicity and efficacy of regorafenib.

13. STUDY COMMITTEES

13.1 Board of Directors

A steering committee will be established, chaired by the lead coordinator. This committee will include the protocol writing committee, the FFCD president, the project manager and the statistician.

13.2 Independent Data Review Committee

An independent monitoring committee will be established, including a physician specializing in oncogeriatrics, a gastroenterologist/oncologist, a statistician and a pharmacovigilance expert. Their functions will be described in the charter of the independent monitoring committee. It will analyze all safety data during the study. It will meet 3 months after the inclusion of the fifteenth patient. In case of unexpected toxicity, unacceptable the independent committee may recommend:
- A protocol amendment that could significantly improve treatment tolerability
- Premature termination of the study if the treatment causes intolerable side effects.

13.3 Centralized proofreading

A panel of radiologists will be responsible for centralized review of radiological imaging collected during the study to determine treatment responses and progressions.

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Ref Type: Abstract

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15. ADMINISTRATIVE CONSIDERATIONS

Study sponsor

The sponsor of the study is the Fédération Francophone de Cancérologie Digestive (FFCD). The study was registered under the EudraCT number: 2015-002086-29.

Reminder of the texts in force

This test will be conducted according to the French law in force

Liability Insurance

Insurance has been taken out by the promoter with SHAM (Société Hospitalière d'Assurances Mutuelles) under contract number XXX (Appendix 11), in accordance with Article L 1121-10 of the Public Health Code.

Request for authorization to the CPP and ANSM

This protocol received the favorable opinion of the CPP (Committee for the Protection of Persons) Ile de France VIII, on 29/06/2015 (Appendix 12).
This protocol has been authorized by the ANSM (Agence Nationale de Sécurité du Médicament) (Appendix 13).

Collection of the patient's consent

The investigator undertakes to collect, after information, the clinical consent of the patient in writing (information sheet and consent form in Appendix 1). A copy of these consents must be kept by the investigator for 15 years, to be presented to the supervisory authorities in case of inspection. The original should be given to the patient.
In accordance with the recommendations of the Cancer Plan (Measure 4.3.), this document has been submitted for review, advice and guidance to the Patients' Committee for Clinical Research (PCCR) of the National League Against Cancer.

Hospital management information and research agreement

Prior to the implementation of the study, the hospital management will be informed by the sponsor of the investigator's interest in participating in this trial.
A research agreement will be established between the administrator of the investigating center and the sponsor.

Data archiving

The files will remain confidential and can only be consulted under the responsibility of the doctors in charge of the patients. The sponsor and the health authorities in case of inspection will have direct access to these documents.
At the end of the trial, the observation book will be kept for 15 years by the investigator.

Computer support

In accordance with the text of the law n° 78-17 of January 6, 1978 modified by the law of August 9, 2004, relating to data processing, files and freedoms, the data of the trial will be recorded in a computerized database of the FFCD Randomization and Analysis Management Center, excluding elements relating to the identity of patients. The FFCD has made a simplified declaration (MR01) to the CNIL for the implementation of its centralized databases.

Data processing

The FFCD's Center for Randomization, Management and Analysis (CRGA) will be responsible for data management and analysis.

Monitoring, quality assurance and inspections by authorities

The investigator agrees in advance that the records of the patients included in the study may be consulted by an FFCD CRA or a person mandated by the sponsor or the FFCD and/or by the health authorities to carry out an audit. On-site visits of the files, scheduled after agreement of the investigator, will take place during the protocol period of the study.

16. PUBLICATION RULES

They shall be in accordance with those established by the FFCD (Appendix 10).

17. APPENDICES

ANNEXE 1 : Notice d'information et formulaire de consentement éclairé pour l'étude clinique
APPENDIX 2: "Patient" self-questionnaire
APPENDIX 3: "Team" Questionnaire
APPENDIX 4: RECIST 1.1 Criteria
APPENDIX 5: ECOG
APPENDIX 6: Measurement of creatinine clearance using the Cockcroft and Gault formula
APPENDIX 7: NCI-CTC Toxicity Criteria Version 4.0
APPENDIX 8: Regorafenib CPR
APPENDIX 9: RSI form
APPENDIX 10: FFCD Publication Rules
SCHEDULE 11: Certificate of Insurance
APPENDIX 12: Favourable opinion of the PPC
APPENDIX 13: Authorization from the ANSM