PARTENARIAT DE RECHERCHE EN ONCOLOGIE DIGESTIVE

PRODIGE 25 (FFCD 11-01) - FOLFA

RANDOMIZED PHASE II STUDY EVALUATING AFLIBERCEPT IN COMBINATION WITH THE LV5FU2 REGIMEN IN FIRST-LINE TREATMENT OF NON-RESECTABLE METASTATIC COLORECTAL CANCER

EudraCT No. 2014-001837-10

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LIST OF ABBREVIATIONS

ALAT	Alanine aminotransferase (or SGPT: serum glutamic pyruvic transaminase)
ANSM	National Agency for the Safety of Medicines and Health Products
ASAT	Aspartate-aminotransferase (or SGOT: serum glutamic oxaloacetic transaminase)
ASCO	American Society of Clinical Oncology
BPC	Good Clinical Practice
GMP	Good Manufacturing Practices
PPC	Committee for the Protection of Persons
CI	Investigator's binder
CISD	Independent Data Monitoring Committee
CO	Observation booklet
CRB	Biological Resource Center
RTA	Translational Research Committee
CTC	Common Toxicity Criteria
DCI	International non-proprietary name
DPD	dihydropyrimidine dehydrogenase
ECG	Electrocardiogram
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
EI	Adverse event
ISG	Serious adverse event
5FU	5-fluorouracil
FFCD	French-speaking Federation of Digestive Oncology
FNCLCC	National Federation of Cancer Centres
HCG	Human chorionic gonadotropin
HR	"Hazard ratio
HTA	Hypertension
IC	Confidence interval
IHC	Immunohistochemistry
MRI	Magnetic resonance imaging
IV	Intravenous
j	Day
LDH	Lactate dehydrogenase
LSN	Upper limit of normal
LV	Leucovorin (= folinic acid)
N	Normal
NCI-CTCAE	National Cancer Institute - Common Toxicity Criteria for Adverse Events
NFS	Blood count
WHO	World Health Organization
PAL	Alkaline phosphatases
PA	Blood pressure
PAD	Diastolic blood pressure
NOT	Systolic blood pressure
PNN	Neutrophils
SG	Overall survival
SSP	Progression-free survival
CT	CT scan
TP	Prothrombin level
TS	Thymidylate synthase
UICC	International Union Against Cancer
Vs	Versus

PROTOCOL ACCEPTANCE FORM

PRODIGE 25 (FFCD 11-01) - FOLFA: Randomized phase II study evaluating aflibercept in combination with LV5FU2 as first-line treatment for unresectable metastatic colorectal cancer

Eudract No. 2014-001837-10

Version 3.0 of 30.06.2014

This version of the protocol is approved by :

The Promoter: Ms. Cécile GIRAULTDate : 30.06.2014Signature :

The Coordinator: Dr Jean Louis LEGOUXDate : 30.06.2014

:

I, the undersigned, Doctor : .....

After having read the requirements of this research, the protocol and its appendices, I hereby certify that I will conduct this trial in compliance with Good Clinical Practice and in accordance with the applicable provisions of the Public Health Code.

In particular, I agree to:

- to respect the protocol as well as all modifications notified to me by the Promoter
- agree to supervise the research in the center and to train my collaborators in the conduct of the research and to provide a nominal list
- have each patient sign a written consent after having read the information note intended for him/her, before any research is carried out
- Report serious adverse events or developments within 24 hours of learning of them, and as specified in the protocol
- respect the inclusion and non-inclusion criteria, as well as the start and end dates of the study
- participate in the biological part of the study and send the samples according to the recommendations
- complete all the items in the observation book, ensure the quality of the data collection and the proper management of the products
- Retain research data and documents for 15 years after the study is completed
- inform the Sponsor of any conflict of interest situation that may affect my scientific independence in the context of the research
- inform the Sponsor without delay of any action, whether amicable or contentious, brought by a person involved in the research or his or her beneficiaries, which may call into question the responsibility of the Sponsor
- accept periodic visits by the Sponsor's representatives, and make available to them all source documents and materials related to the research in order to ensure quality control of the data recorded in the case report book. I agree to an audit by the Sponsor or one of its representatives and/or an inspection by the health authorities.
- respond by phone or mail to requests for corrections or clarifications regarding the observation book
- Allow time for the ARC FFCD to sign the forms, answer any questions and take action

Date: Signature:

STAMP of the CENTER :

Send the original to the CRGA of the FFCD - 7 bd Jeanne d'Arc - BP 87900 - 21079 Dijon Cedex

SYNOPSIS

Title of the study	**Randomized phase II study evaluating aflibercept in combination with LV5FU2 as first-line treatment for unresectable metastatic colorectal cancer**
Judging criteria	**Principal:** - Rate of patients alive and without radiological progression within 6 months (RECIST 1.1) by investigator
	Secondary: - Tolerance of LV5FU2- aflibercept combination (NCI-CTC v4.0) - Quality of life: EORTC QLQ-C30 and time to definitive deterioration in quality of life - Overall survival at 1 and 3 years - Best response to study treatment (RECIST V1.1) by investigator at 1 year - Rate of patients alive and without radiological progression within 6 months (RECIST 1.1) by centralized review - Rate of alive patients without radiological progression at 1 year (RECIST 1.1) by investigator - Rate of patients alive and without clinical and/or radiological progression at 6 months and 1 year by investigator - Resectability for curative purposes at 1 year - Prognostic character of thymidylate synthase (TS) polymorphisms within 6 months
Inclusion criteria	- Age ≥ 65 years - General condition WHO < 2 - Histologically proven metastatic adenocarcinoma of the rectum or colon on the primary tumor or a metastasis, unresectable and/or non-operable patient - Non or minimally symptomatic metastases - At least one measurable target according to RECIST v1.1 criteria not previously irradiated - No prior treatment of metastatic disease. Prior chemotherapy in the adjuvant setting completed 6 months or more prior to diagnosis of metastasis is allowed - Adequate laboratory workup: Hb ≥ 9 g/dl, neutrophils ≥ 1500 /mm^3 , platelets ≥ 100,000/mm^3 , total bilirubin ≤ 1.5 LSN, creatinine clearance > 50 mL/min (Cockroft and Gault formula), creatinine level < 1.5 x LSN, PAL < 5 x LSN, AST and ALT ≤ 5 x LSN, GGT < 5x LSN - Proteinuria (dipstick) < 2+; if ≥ 2+, do 24-hour proteinuria which should be ≤1g, - Patients treated with anticoagulants (coumadin, wafarin) are eligible for inclusion if close monitoring of INR can be performed. A change of anticoagulant treatment to a low molecular weight heparin is preferable if the indications are respected - Centralized genotyping of thymidylate synthase (TS) on blood DNA - Patient who signed the informed consent
Criteria for non-inclusion	- Patients whose primary tumor is symptomatic and in place (occlusion; hemorrhage) - Presence of brain metastases, uncontrolled spinal cord compression, carcinomatous meningitis, signs of brain or leptomeningeal involvement - Macro-nodular peritoneal carcinosis (risk of perforation) - Uncontrolled hypercalcemia - Uncontrolled hypertension (SBP >150 mm Hg and DBP >100 mm Hg) or history of hypertensive crisis or hypertensive encephalopathy - Progressive disease not balanced during the last 6 months: hepatic insufficiency, renal insufficiency, respiratory insufficiency - Myocardial infarction, severe/unstable angina, coronary artery bypass grafting, NYHA class III or IV congestive heart failure, stroke, or transient ischemic attack in the 6 months prior to inclusion - The following conditions within 3 months prior to inclusion: grade 3 or 4 gastrointestinal bleeding/hemorrhage, treatment-resistant peptic ulcer, ulcerated esophagitis or gastritis, infectious or inflammatory bowel disease, diverticulitis, pulmonary embolism or other uncontrolled thromboembolic event, unhealed bone fractures - Major surgery within 28 days of starting treatment - Known acquired immunodeficiency syndrome (AIDS-related illnesses) or known HIV infection requiring antiretroviral therapy

	- History of hematologic malignancy or cancer except those treated for more than 5 years and considered cured, carcinoma *in situ* of the uterine cervix and treated skin cancers (excluding melanoma) - Any contraindication to the drugs used in the study - Known DPD deficiency - Patients treated with the new oral anticoagulants (such as rivaroxaban XARELTO®, apixaban ELIQUIS®, dabigatran PRADAXA®) unless they are being replaced by VKAs - Impossibility to undergo the medical follow-up of the trial for geographical, social or psychological reasons
Study design and treatment plan	Phase II, open-label, randomized, multicenter study. Patients will be treated every 14 days with: - LV5FU2 simplified every 2 weeks: folinic acid 400 mg/m^2 IV over 90 min, then 5FU 400 mg/m^2 IV bolus at D1, followed by continuous infusion of 5FU 2400 mg/m^2 over 46 h. - Preceded or not by an IV infusion of aflibercept 4 mg/kg over 1 hour
Duration of treatment	Until progression or unacceptable toxicity
Stratification	A 1 : 1 randomization by minimization will be performed according to the following stratification factors: - Center - Age: $\leq$ 75 years vs > 75 years - TS-5'UTR polymorphism of thymidylate synthase: 2R2R-2R3R versus 3R3R genotype - Metastatic site: 1 vs > 1
Statistical methodology	All analyses will be performed on a modified intention-to-treat basis. Quantitative variables will be described using the median, mean, standard deviation of the mean, inter-quartile range, minimum and maximum. Qualitative variables will be described by their frequency, the 95% confidence interval will be calculated using the exact method. Overall survival and progression-free survival curves will be estimated using the Kaplan-Meier method.
Sample calculation and justification	In the FFCD 2000-05 study using LV5FU2 in the same indication, the median progression-free survival was 5.7 months. Hypothesis: H_0 : A 6-month live progression-free rate of 40% or less is considered unattractive. H_1 : a rate of patients alive and progression-free at 6 months of more than 40% is necessary to consider the treatment interesting; a progression-free survival rate at 6 months of 60% is expected. With a one-sided alpha risk of 5%, 56 evaluable patients in each arm (total 112 patients) would need to be included to achieve 90% power under the considered H1 hypothesis (calculations using the exact binomial distribution). If 29 or more patients are alive and not progressing at 6 months, the efficacy of the treatment arm studied can be considered interesting.
Expected number of patients	Taking into account a 5% rate of lost to follow-up, **118 patients** (59 patients per group) should be included
Ancillary study	Study of Treg lymphocytes in blood samples and study of VEGF receptors in tumor samples
Planned study period	**Theoretical start date of inclusions: January 2015** **Theoretical end date of inclusions: December 2017** **Final study analysis: July 2018**

EXAMINATION AND FOLLOW-UP SCHEDULE

	BEFORE TREATMENT	DURING TREATMENT and if treatment is stopped without progression			AFTER STOPPING FIRST-LINE TREATMENT (progression)
	Within 3 weeks prior to randomization	Before each course of LV5FU2	Every 8 weeks Even if spaced for toxicity	End of treatment consultation (30 days after the date of the last administration)	Every 3 months for 2 years then every 6 months for 1 year
Clinical and biological informed consent	X				
CLINICAL EXAMINATION					
Weight, height, body surface area, blood pressure	X	X	X	X	X
General status WHO	X	X	X	X	X
Quality of Life Questionnaire (QLQ-C30)	X		X	X	
Toxicity Assessment NCI-CTC V4.0	X****	X	X	X	X
ECG	X				
MORPHOLOGICAL EXAMINATIONS					
Spiral thoracoabdomino-pelvic CT (TAP) without and with injection or MRI injected with gadolinium + non-injected thoracic CT	X***		X***		
BIOLOGICAL ASSESSMENT					
Biological check-up	X*	X**	X*	X**	
ACE marker	X		X		X
BIOLOGICAL STUDY					
Determination of the 2R2R-2R3R versus 3R3R mutation of thymidylate synthase - 2 EDTA tubes (5 mL of blood) (Georges Pompidou European Hospital - Biochemistry Laboratory Dr LORIOT)	X				
Prognostic value of Treg lymphocytes - 3 x 10 mL heparinized tubes (Georges Pompidou European Hospital - INSERM - Dr TERME)	X (before the 1ière treatment)	Before the 3ième treatment (D28 before administration)			
KRAS and BRAF status To be completed by the centers and entered in the CRF	X				

*: Complete biological check-up: CBC/platelets, blood ionogram, Ca^{2+} , Mg^{2+} , creatinine, albumin, PT, AST, ALT, alkaline phosphatases, total, free and conjugated bilirubin, LDH, proteinuria (+ 24 hour proteinuria if $\geq$ 2+), INR

** Biological check-up before each course of chemotherapy: CBC, platelets, creatininemia, proteinuria (dipstick) + 24-hour proteinuria if ≥ 2+, INR strongly recommended for patients on AVK
*** : An anonymized copy of the imaging is to be sent to the FFCD for centralized review (inclusion CT scan + 3 evaluation CT scans)
**** : Search for pre-existing symptoms at inclusion

1. Objectives of the study

1.1 Main objective

The primary objective of the study is to evaluate the efficacy of aflibercept combined with 5FU monotherapy by considering the rate of patients alive and without radiological progression at 6 months according to the investigator.

1.2 Secondary objectives

The secondary objectives of the study are to evaluate:

- Safety of aflibercept in combination with 5FU and folinic acid (NCI CTC v4.0)
- Quality of life according to the EORTC QLQ-C30 score and time to definitive deterioration in quality of life
- Overall survival at 1 and 3 years
- The rate of patients alive and without radiological progression within 6 months (RECIST 1.1) according to the centralized review
- The rate of patients alive and without radiological progression at 1 year (RECIST 1.1) according to the investigator
- The rate of patients alive and without clinical and/or radiological progression within 6 months and at 1 year by investigator
- The best response to study treatment (RECIST 1.1 criteria) at 1 year according to the investigator
- Resectability for curative purposes at 1 year

We will try to confirm the prognostic character of the *TS-5'UTR* genotype of thymidylate synthase on the main criterion of the study, on both treatment arms combined.

2. Patient selection

2.1 Inclusion criteria

- Age ≥ 65 years
- General condition WHO less than 2
- Histologically proven metastatic adenocarcinoma of the rectum or colon on the primary tumor or a metastasis, unresectable and/or non-operable patient
- Non or minimally symptomatic metastases
- At least one measurable target according to RECIST v1.1 criteria not previously irradiated
- No prior treatment of metastatic disease. Prior chemotherapy in the adjuvant setting completed 6 months or more prior to diagnosis of metastasis is allowed
- Adequate laboratory workup: Hb ≥ 9 g/dl, neutrophils ≥ 1500 /mm^3 , platelets ≥ 100 000/mm^3 , total bilirubin ≤ 1.5 ULN, creatinine < 1.5 x ULN, creatinine clearance > 50 mL/min (Cockroft and Gault formula), PAL < 5 x ULN, AST and ALT ≤ 5 x ULN, GGT < 5 x ULN
- Proteinuria (dipstick) < 2+; if ≥ 2+, do 24-hour proteinuria which should be ≤ 1 g,
- Patients treated with anticoagulants (coumadin, wafarin) are eligible for inclusion if close monitoring of INR can be performed. A change of anticoagulant treatment to a low molecular weight heparin is preferable if the indications are respected
- Genotyping of thymidylate synthase (TS) on blood DNA
- Patient who signed the informed consent

2.2 Non-inclusion criteria

- Patients whose primary tumor is symptomatic and in place (occlusion; hemorrhage)
- Presence of brain metastases, uncontrolled spinal cord compression, carcinomatous meningitis, signs of brain or leptomeningeal involvement

- Macro-nodular peritoneal carcinosis (risk of perforation)
- Uncontrolled hypercalcemia
- Uncontrolled hypertension (SBP >150 mmH and DBP >100 mmHg) or history of hypertensive crisis or hypertensive encephalopathy
- Any progressive disease not balanced during the last 6 months: hepatic insufficiency, renal insufficiency, respiratory insufficiency
- Myocardial infarction, severe/unstable angina, coronary artery bypass grafting, NYHA class III or IV congestive heart failure, stroke, or transient ischemic attack in the 6 months prior to inclusion
- The following conditions within 3 months prior to inclusion: grade 3 or 4 gastrointestinal bleeding/hemorrhage, treatment-resistant peptic ulcer, ulcerated esophagitis or gastritis, infectious or inflammatory bowel disease, diverticulitis, pulmonary embolism or other uncontrolled thromboembolic event, unhealed bone fractures
- Major surgery within 28 days of starting treatment
- Known acquired immunodeficiency syndrome (AIDS-related illnesses) or known HIV infection requiring antiretroviral therapy
- Anti-tumor treatments other than those in the study (chemotherapy, targeted therapy, immunotherapy)
- History of hematologic malignancy or cancer except those treated for more than 5 years and considered cured, carcinoma *in situ* of the uterine cervix and treated skin cancers (excluding melanoma)
- Any contraindication to the drugs used in the study
- Known DPD deficiency
- Patients treated with the new oral anticoagulants (such as rivaroxaban XARELTO®, apixaban ELIQUIS®, dabigatran PRADAXA®) unless they are being replaced by VKAs
- Impossibility to undergo the medical follow-up of the trial for geographical, social or psychological reasons

3. INCLUSION ASSESSMENT

3.1 Assessment of the disease

The inclusion assessment is to be performed within 3 weeks prior to randomization. It includes:

Full clinical examination:
- Description of clinical signs related to the tumor disease
- Weight, height, body surface
- Blood pressure (SAP and DBP)
- General status WHO
- Possible history of venous thrombosis, 5-FU toxicity, and treated hypertension

Biological check-up:
- Blood count (hemoglobin, PNN, platelets), creatinine level, blood ionogram, calcium level, PT, albumin level, total, free and conjugated bilirubin level, transaminases, alkaline phosphatases, LDH, proteinuria (urine dipstick) and 24h proteinuria if dipstick $\geq$ 2+.
- Sampling for biological research study (thymidylate synthase, Treg lymphocyte; see chapter 8)
- Marker : ACE

Morphological evaluation of the tumor:
- Spiral thoracoabdomino-pelvic (TAP) scan, without and with contrast injection, performed **no more than 3 weeks before randomization**.
  In case of contraindication to iodinated contrast injection, a hepatic or abdominal MRI with gadolinium injection and a thoracic CT scan without injection can be performed.
  Morphological examinations should be the same throughout the patient's follow-up.
  Make an anonymized copy of the images to be sent to the CRGA of the FFCD for centralized review.

Quality of Life Questionnaires:
- QLQ-C30 questionnaire completed

Search for thymidilate synthase (TS) polymorphisms (blood)

- It will be done in the biochemistry department of the Georges Pompidou European Hospital. The investigator will send 2 EDTA tubes of 5mL of the patient's blood according to the pre-established regulatory procedures (see chapter 8: biological logistics). The results will be faxed to the investigator within 10 working days.

RAS and BRAF status

- They will be performed routinely in each center and the results collected in the observation booklet.

Biological study on the prognostic value of Treg lymphocytes:

- ième3 x 10 mL heparinized blood tubes before the first treatment and 3 x 10 mL heparinized blood tubes before the third treatment (see chapter 8)
- Establishment of a collection of tumor samples for pooled analysis with other studies (see Chapter 8)

4. RANDOMIZATION

4.1 Randomization of patients

- As soon as a patient is selected to enter the study, he/she is informed and asked to accept and sign the informed consent form. This consent mentions the determination of the thymidilate synthase polymorphism on his lymphocytes (blood sample), the study of regulatory T lymphocytes and vascular growth factors

- A blood sample is taken and sent to the biochemistry department of the Georges Pompidou European Hospital. These samples will later be sent to the FFCD's EPIGENETEC BRC for archiving.

- With the result of the thymidilate synthase polymorphism, the investigator can randomize the patient according to the stratification factors defined for the study

- WHO general status will be checked with the patient, possibly by telephone consultation, within 48 hours prior to randomization

The randomization will be carried out by the CRGA of the FFCD after reception of the fax of randomization (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.

The randomization number and treatment arm will be communicated to the investigator and the pharmacist by return fax.

After randomization of the patient, treatment should be started within a maximum of 2 weeks.

An observation booklet will be sent at the opening of the center. An observation booklet will be sent after each randomization.

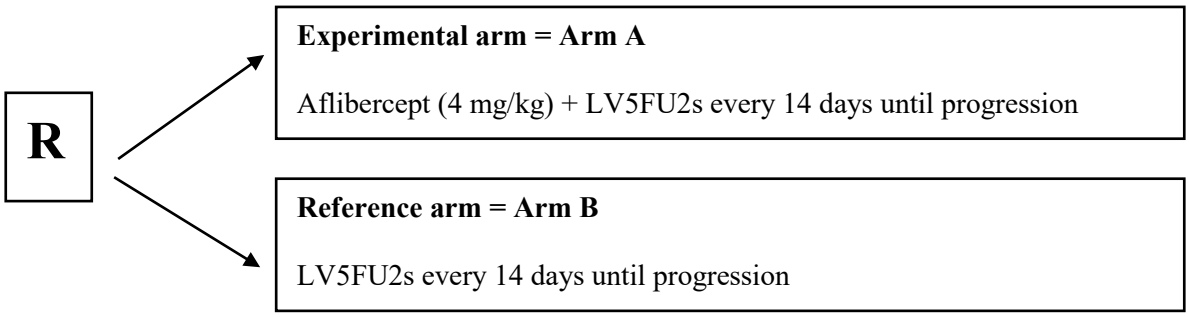
The 1ière randomization in a center will trigger the dispatch of aflibercept treatment. Aflibercept stock management for subsequent inclusions will be done by the center's pharmacy.

4.2 Stratification

A 1:1 randomization by minimization will be performed according to the following stratification factors:

- Center
- Age: ≤ 75 years vs > 75 years
- TS-5'UTR polymorphism of thymidylate synthase: 2R2R-2R3R versus 3R3R genotype
- Metastatic site: 1 vs > 1

5. DIAGRAM OF THE STUDY

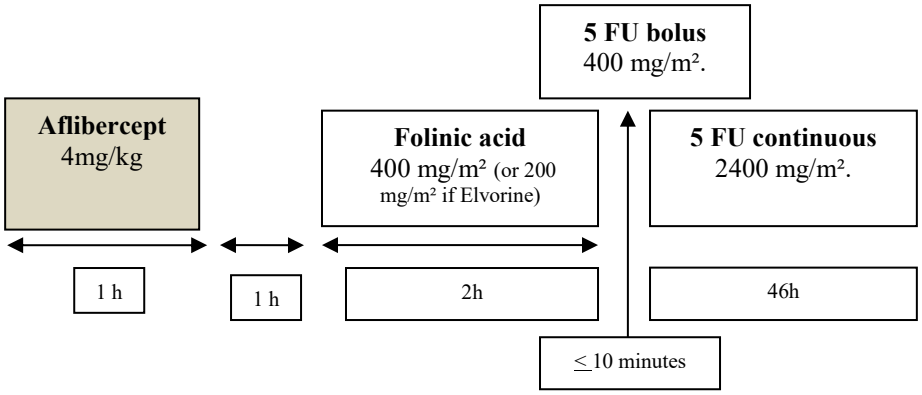


6. TREATMENT

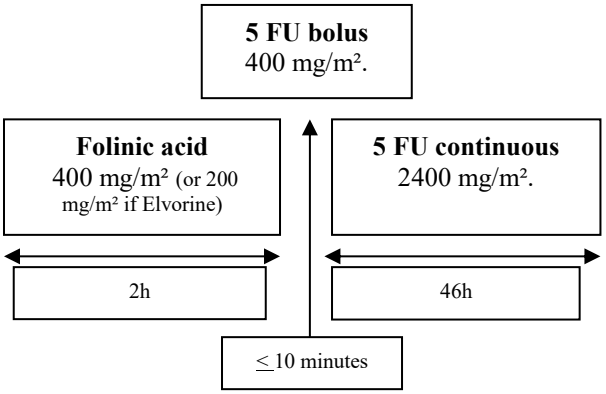
In this academic research, the drugs for the LV5FU2 treatments (drugs with MA used in their indication) will be taken from the hospital stock in accordance with article L1121-16-1 of the Public Health Code.

Aflibercept will be provided as part of the study.

The traceability of the products will be ensured by the pharmacies.



ARM A: LV5FU2s + aflibercept administration scheme



ARM B: LV5FU2s administration scheme

6.1 Administration of aflibercept (arm A)

Aflibercept [25 mg/mL IV infusion solution - 8 mL vials (200 mg/vial)], should be administered at the beginning of each chemotherapy course. Vials should be stored in the refrigerator at 2-8°C in the original packaging and protected from light.

Aflibercept will be administered at 4 mg/kg and should be diluted directly into the infusion bag (100ml) with sterile 0.9% sodium chloride or G5%. Diluted solutions should be administered using infusion sets with a 0.2 micron polyethersulfone filter. Infusion sets should be made of one of the following materials: polyvinyl chloride (PVC) containing bis(2ethylhexyl-) phthalate -(DEHP), DEHP-free PVC containing trioctyl trimellitate (TOTM), polypropylene, polyethylene-lined PVC or polyurethane. Note: Polyvinylidene fluoride (PVDF) or nylon filters should not be used.

The solution should be prepared in a sterile environment.
Aflibercept should be administered over 1 hour. The preparation should not exceed 2 hours at room temperature (25°C).

Male patients should use contraception for the duration of treatment and for up to 6 months after discontinuation of treatment.

6.2 Administration of simplified LV5FU2 (arms A and B)

Folinic acid is administered as an IV infusion at a dose of **400 mg/m² (or 200 mg/m² if Elvorine)** over 2 hours.
The **5 Fu bolus** is administered within 10 minutes at **400 mg/m²** in 100 cc of G5%.
Continuous 5-Fu is administered IV at a dose of **2400 mg/m²** over 46 hours.

6.3 Modifications to treatment modalities based on tolerance

6.3.1 Aflibercept

In the event of aflibercept-related toxicity, dose adjustments should be made based on the highest grade of toxicity observed according to the NCI-CTC version 4.0 scale.
If the patient has multiple toxicities, the adjustment will be made according to the highest toxicity.
Once the dose has been decreased, it is not permitted to increase it again.

Aflibercept should be administered if PNN $\geq$ 1400/mm^3 and platelets > 90,000/mm^3 and after recovery to a grade $\leq$ 1 for all other toxicities (except alopecia). If there is a recurrence of febrile neutropenia or neutropenic sepsis after 5FU dose reduction, consideration may be given to reducing the aflibercept dose to 2 mg/kg (see Product Monograph).

Toxicity	Grade (NCICTC V4.0)	Action
Hypertension	**Grade $\leq$ 2**	Initiate antihypertensive therapy or modify antihypertensive therapy if necessary. No change in dose, no postponement of treatment
	Grade 3 (requiring more than one antihypertensive treatment or requiring intensification of antihypertensive treatment)	Postpone LV5FU2 and aflibercept (maximum 2 weeks), until recovery of BP (blood pressure) $\leq$ 140/90 or to a SBP < 160 if DBP <90 for patients with known history of isolated systolic hypertension: • If BP is controlled within 2 weeks of deferral ▪ 1ier event: re-administer LV5FU2 and aflibercept at the same dose ▪ 2ième episode: re-administer LV5FU2 at the same dose and re-administer aflibercept at **2 mg/Kg** ▪ 3ième event: permanent discontinuation of aflibercept, resumption of LV5FU2 • If after 2 weeks of deferral BP is still not controlled despite antihypertensive treatment: restart LV5FU2 at the same dose and stop aflibercept for one cycle of LV5FU2 (14 days). Re-evaluate BP at the next cycle and restart aflibercept at **2 mg/kg** if BP controlled. • In the event of recurrence of Grade 3 despite optimal antihypertensive therapy and aflibercept dose reduction, or if BP is still uncontrolled despite aflibercept deferral for 2 weeks (4 weeks after the last administration): DEFINITELY STOP aflibercept. LV5FU2 can be continued.
	Grade 4	When hypertension is accompanied by symptoms of organ failure such as hypertensive retinopathy, impaired renal

		function (such as increased proteinuria), symptoms of cardiovascular or central nervous system morbidity, aflibercept should be discontinued. DEFINITIVE WITHDRAWAL of aflibercept and cardiological advice

Toxicity	Grade (NCI-CTC v4.0)	Action
Arterial thromboembolic event	Whatever the grade	DEFINITELY DISCONTINUE aflibercept
Venous thromboembolic event	Grade 3	1ier episode: treatment with heparin and continuation of ablibercept[1] 2ième episode despite appropriate anticoagulant therapy: DEFINITELY STOP aflibercept
	Grade 4	DEFINITELY DISCONTINUE aflibercept[2]
Hemorrhage	Grade 3-4	DEFINITELY DISCONTINUE aflibercept
Intestinal perforation/fistula formation at any anatomical site	Whatever the grade	DEFINITELY DISCONTINUE aflibercept
Reversible posterior leukoencephalopathy syndrome[3]	Whatever the grade	DEFINITELY DISCONTINUE aflibercept

[1] After evaluation of the risk of extension and/or embolism according to the investigator's judgment
[2] Continuation of aflibercept may be considered, depending on the benefit/risk balance, in the event of secondary discovery of asymptomatic pulmonary embolism
[3]Appearance of vasogenic edema of the white matter and predominant in the posterior parieto-occipital regions: symptoms: Acute and abrupt HTA (DBP > 120mmHg), psychomotor slowing, headache, confusion, restlessness, lethargy, nausea, vomiting, convulsions (initially focal), transient coma, memory disturbances, visual disturbances (blurred vision, scintillating scotoma, visual neglect, hemianopsia, cortical blindness)

Proteinuria
A urine dipstick test should be performed prior to each administration of aflibercept (protein, red blood cells, leukocytes):

- If proteinuria is < 2+ and there is no hematuria, aflibercept can be administered
- If proteinuria is ≥ 2+, aflibercept should be withheld and reintroduced as soon as 24-hour proteinuria is < 2g. If proteinuria ≥ 2g/24h recurs, aflibercept should be withheld until 24-hour proteinuria < 2g and reintroduced at **2 mg/kg**

Aflibercept should be permanently discontinued if the patient develops nephrotic syndrome or thrombotic microangiopathy, suspected on the basis of proteinuria-hematuria.

The 24-hour proteinuria assay can be replaced by the ratio of urine urea to creatinine on morning voiding, expressed in mg/dl. If this ratio is > 1, 24-hour proteinuria should be measured. If it is greater than 2, a nephrological opinion should be sought.

Hypersensitivity reaction to aflibercept

Severity of the symptom	Recommendation
Light and moderate	SUSPEND the aflibercept infusion

Example: Grade ≤ 2: skin reaction, pruritus, flush, rash, dyspnea, tachycardia, hypotension, anxiety, headache, myalgia, edema, nausea	- Administer diphenydramine 50 mg IV and/or dexamethasone 10 mg IV - Resume aflibercept infusion after recovery
Severe Example: symptomatic bronchospasm, generalized urticaria, PAS ≤ 80 mmHg, angioedema, anaphylaxis	STOP aflibercept infusion - Administer diphenydramine 50 mg IV and/or dexamethasone 10 mg IV and/or epinephrine if necessary - DEFINITELY DISCONTINUE aflibercept

Unhealed wound/surgery

The ½ life of aflibercept is approximately 20 days. Suspend aflibercept at least 4 weeks before any surgery.

Aflibercept should be administered at least 4 weeks after surgery and after complete healing.

For minor procedures (implantable chamber placement, biopsies, tooth extraction), aflibercept can be reintroduced as soon as healing is complete.

Aflibercept should be permanently discontinued if there is a wound opening or failure of a wound to heal requiring medical intervention.

6.3.2 Chemotherapy

Before each treatment, the following should be checked: blood count, creatinine level, proteinuria (urine dipstick) and 24-hour proteinuria if dipstick ≥ 2+. Proteinuria may be omitted if LV5FU2 is administered without aflibercept. Chemotherapy will be started if:

- PNN≥ 1400/mm^3
- Plates≥ 90 000/mm^3
- Hemoglobin≥ 9.5 g (if necessary after transfusion)

The chemotherapy course will be delayed by one week: in case of moderate hematological toxicity (PNN < 1400/mm^3 and/or platelets < 90,000/mm^3), persistent digestive toxicity (oral ulcerations, diarrhea, or grade 3-4 esophagitis) or other grade 3-4 toxicity. The dose of 5FU will then be modified according to the instructions in Tables 1 and 2.

In the event of elevated creatinine levels, additional investigations will be carried out by the investigator who will decide whether or not additional therapeutic measures should be taken or if progression on treatment should be diagnosed.

Chemotherapy toxicities are assessed using the NCI CTCAE version 4.0 scale (Appendix 6).

Table 1. Dose **adjustment of** 5-FU for the following courses after a one-week postponement of the course due to toxicity

TOXICITY the day before or the day before the treatment	**5-FU**
PNN≥ 1400, platelets≥ 90 000	100 %
1,000≤ PNN < 1,400 and/or 75,000≤ platelets < 90,000	50% bolus
and/or persistent grade 1 or 2 digestive toxicity	75% continuous infusion
PNN < 1000 and/or platelets < 75 000 and/or persistent grade 3-4 digestive toxicity	No 5FU and 8 day delay

TOXICITY in the intercourse	5-FU
Grade 3-4 febrile neutropenia, Grade 4 neutropenia (PNN < 500), Grade 3-4 thrombocytopenia (<50000) and/or Grade 3-4 digestive toxicity	0% bolus and 75% continuous infusion**.

* Digestive toxicity: mucitis, diarrhea, epigastralgia.
** Provided that there is no residual toxicity on the day of the treatment that would require a further 8-day delay in treatment

Reminder:

Grade 3 febrile neutropenia (NCI CTC V4.0) = presence of decreased neutrophils (any decrease) associated with fever.
Grade 4 febrile neutropenia (NCI CTC V4.0) = decrease in neutrophils (any decrease) associated with life-threatening fever and/or requiring emergency management.

Table 2. Dose adjustment of 5-FU for subsequent courses after a 2ème episode of toxicity, after a 1ère dose reduction and a further one-week delay

TOXICITY the day before or the day before the treatment after a 2ème episode of toxicity, after a first dose reduction and a new postponement of the treatment	5-FU
PNN≥ 1400, platelets≥ 90 000	0 % bolus
1000≤ PNN < 1400 and/or 75000≤ platelets < 90 000	0% bolus and 75% continuous infusion
Isolated persistent grade 1 or 2 digestive toxicity	50% continuous infusion
PNN < 1000 and/or platelets < 75000 and/or persistent grade 3-4 digestive toxicity	No 5FU and 8 day delay
TOXICITY IN THE INTERCOURSE	**5-FU**
Grade 3-4 febrile neutropenia, Grade 4 neutropenia (PNN < 500), Grade 3-4 thrombocytopenia (<50000) and/or Grade 3-4 digestive toxicity	0% bolus and 50% continuous infusion

* Digestive toxicity: mucitis, diarrhea, esophagitis.
** Provided there is no residual toxicity at D21 requiring a further 8-day delay in treatment

No change in folinic acid dose.

6.3.3 Criteria for stopping chemotherapy during treatment

- Major toxicity requiring permanent discontinuation of treatment:
  - If aflibercept-related toxicity requires discontinuation for 4 or more consecutive weeks (i.e., with a margin of 2 days for each 7-day deferral for chemotherapy toxicity, a total of 28 + 8 days = 36 days), then aflibercept is permanently discontinued.
- Serious or unexpected event requiring discontinuation of treatment:
  - In case of discontinuation of aflibercept due to an intercurrent event (radiotherapy, hospitalization for other reasons than toxicity, ...), the resumption of aflibercept will be left to the investigator's choice. The treatment will then be collected within the framework of the study (in the observation booklet).
  - Aflibercept may be discontinued immediately and permanently at the sole discretion of the investigator, if deemed necessary for the patient.

- Refusal to proceed, at the patient's request, or after withdrawal of consent by the patient (to be documented).
- Life-threatening toxic reaction in the opinion of the physician caring for the patient.
- Progressive disease.
- If aflibercept is deferred or discontinued, concurrent chemotherapy (LV5FU2) may be continued as described in this protocol.
- If LV5FU2 chemotherapy is discontinued, aflibercept may be continued as described in this protocol.
- If chemotherapy is deferred for one to three weeks, aflibercept will also be deferred and restarted at the same time as the chemotherapy according to the protocol. Evaluation of chemotherapy toxicity for deferral should be done on a weekly basis to avoid unnecessary delay in restarting chemotherapy.

Patients will be followed until death according to the protocol schedule and treatment types will be collected after progression on the first line of treatment.

6.3.4 Premedications and concomitant treatments

Treatments considered necessary for the well-being of the patient may be administered at the discretion of the investigator.

If anemia occurs, it will be treated according to its mechanism: spoliation, inflammatory or bone marrow failure.

Subcutaneous administration of growth factor is permitted:
- for the treatment of Grade 3-4 febrile neutropenia
- as secondary prophylaxis from day 5 to day 11 after the occurrence of neutropenic events during the previous chemotherapy cycle. These neutropenic events are: grade 3-4 febrile neutropenia, proven infections with concomitant grade 3-4 neutropenia, grade 4 neutropenia > 7 days. **Growth factor will be used for all subsequent cycles.**

6.4 Contraindicated treatments

With 5FU: yellow fever vaccine, live attenuated vaccines, phenytoin for prophylaxis.

7. PATIENT MONITORING

7.1 During treatment

- Before each course of chemotherapy:
- Complete clinical examination: weight, body surface area, general condition WHO, blood pressure
- Biological check-up: CBC, platelets, creatinine, proteinuria (urine dipstick) and 24-hour proteinuria if dipstick ≥ 2+.
- Treg lymphocyte biological study: 3 x 10 mL heparinized blood tubes before the 3ième treatment **(do not collect and send sample on Friday)**
- Toxicity assessment according to NCI-CTC Version 4.0

- Every 8 weeks, even when spaced out for toxicity:
- Clinical examination: Weight, body surface area, general condition, WHO, blood pressure
- Biological check-up: Hemoglobin, PNN, platelets, creatinine, blood ionogram, calcemia, TP, total, free and conjugated bilirubin, transaminases, alkaline phosphatases, LDH, 24-hour proteinuria if urine dipstick > 2+, INR for patients on AVK, ACE
- Morphological evaluation of the disease: (every 8 weeks even after stopping the treatment for toxicity, in order to show the date of progression)

- Spiral thoracoabdomino-pelvic CT scan, without and with contrast injection
- In case of contraindication to iodinated contrast injection, hepatic or abdominal MRI with gadolinium injection and thoracic CT scan without injection.

FOR CENTRALIZED PROOFREADING :
During the first 6 months following the patient's inclusion, send to the FFCD (CD ROM or ARC FFCD) an anonymized copy of each morphological evaluation (i.e. 3 evaluations + inclusion imaging)

- QLQ-C30 Quality of Life Questionnaire completed

7.2 After discontinuation of treatment for progression

Patients will be reviewed in **consultation 30 days +/- 2 days after discontinuation of** study **treatment**:

- Complete clinical examination (weight, general condition WHO, BP)
- Evaluation of toxicities
- Biological workup: CBC, platelets, creatinine, proteinuria (dipstick) + 24-hour proteinuria if > 2+.
- Quality of Life Questionnaire QLQ-C30

Patients will then be seen in **consultation every 3 months** for 2 years and every 6 months for 1 year:

- Clinical examination with search for late toxicities of the first line treatment
- Additional examinations required by their new treatments

CAUTION: Male patients should continue to use effective contraception for at least 6 months after discontinuing treatment.

7.3 After discontinuation of treatment for reasons other than progression:

Patients will be reviewed in consultation **30 days +/- 2 days after stopping the treatment**:

- Complete clinical examination (weight, general condition WHO, BP)
- Evaluation of toxicities
- Biological work-up: CBC, platelets, creatinine, proteinuria (dipstick) + 24-hour proteinuria if > 2+.
- Quality of Life Questionnaire QLQ-C30

Patients will then be seen in consultation **every 2 months until progression**, with :

- Clinical examination with search for late toxicities of the first line treatment
- Additional examinations required by their new treatments
- Evaluation of the progression (biological and morphological protocol examinations every 8 weeks).

After progression, patients will be seen in consultation every 3 months for 2 years and then every 6 months for 1 year (see chapter 7.2).

CAUTION: Male patients should continue to use effective contraception for at least 6 months after discontinuing treatment.

8. ORGANIC LOGISTICS

8.1 Determination of Thymidylate Synthase polymorphisms (required for randomization)

Required samples

2 x 5 ml EDTA tubes of blood at the time of inclusion.

Shipment of the tubes, via the DHL box provided at the opening of the center to :

Dr Marie-Anne LORIOT
Biochemistry Laboratory
Georges Pompidou European Hospital (HEGP)
20 Le Blanc Street
75015 PARIS

Use only the DHL box containing the DHL slip **for the HEGP Biochemistry Laboratory.**

After sending this box, the box necessary for the inclusion of the next patient will be sent to the investigating center.

8.2 Study of Treg lymphocytes

Required samples

3 x 10 ml heparinized tubes of blood

- before the administration of the first cycle of chemotherapy (except on Fridays)
- before the third cycle of chemotherapy, on the patient's arrival, avoiding Friday

Sampling kits will be sent to each center upon opening (2 DHL boxes each containing 3 x 10 mL heparinized tubes and the *appropriate* forms).

The tubes must be delivered to the laboratory and packaged within 24 hours. This is why shipments should not be made on Friday.

These samples will be sent at room temperature by specialized carrier (DHL) to :

Ms. Magali TERME
INSERM U970 unit, team 10,
PARCC-HEGP
56 Leblanc Street
75015 PARIS

For these samples before C1 and before C3, use only the DHL boxes containing the delivery note **to the INSERM HEGP unit.**

After each shipment of a DHL box, a new DHL box will be sent for subsequent patients.

Summary of blood samples:

Withdrawals	Before randomization	Before C1	Before C3
TS (required for randomization)	2 x 5 mL EDTA tubes		
Treg lymphocytes and vascular growth factors		3 x 10 mL heparinized tubes	3 x 10 mL heparinized tubes

DHL box	Address : Mme Loriot HEGP - Laboratoire de Biochimie 20 rue Le Blanc 75015 PARIS	Address to be sent to: Mme Terme HEGP - Unité INSERM U970-équipe 10 56 rue Le Blanc 75015 PARIS	Address to be sent to: Mme Terme HEGP - Unité INSERM U970-équipe 10 56 rue Le Blanc 75015 PARIS

8.3 Tumor sample

One paraffin-embedded tumor block or 2-3 paraffin-embedded diagnostic biopsies

Shipping kit

Upon receipt of the form indicating the number of biopsies or tumor blocks to be sent, you will receive a pre-stamped max letter that will allow the samples to be shipped.
These samples will be sent to :

Pr Pierre LAURENT-PUIG
CRB Epigenetec, INSERM Unit U775
45 rue des Sts Pères
75006 PARIS

8.4 Storage of blood samples

The samples, once the TS determination has been carried out at the HEGP, will be transferred to the FFCD Biological Resource Center, named EPIGENETEC (45 rue des Saints Pères, 75006 PARIS), directed by Pr Pierre LAURENT PUIG. They will be stored there for the time necessary to set up the subsequent analyses.

Constitution of a collection of tumor samples at the FFCD's biological resource center (EPIGENETEC) for grouped analysis with those of other studies (see Chapter 8).

9. MANAGEMENT OF SERIOUS ADVERSE EVENTS (SIA)

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, by regular blood tests. Toxicities will be assessed using the NCI-CTC-AE version 4.0 toxicity scale (see Appendix 6).
In case of an emergency, the patient, his family or his physician should call the investigator to inform him of an event.

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 case report form on the "toxicity" pages provided for this purpose, up to 30 days after the last administration and beyond if related to the study products. The most severe grade of the intercourse will be recorded in the case report form (NCI-CTC version 4 or severity grade according to the investigator's judgment when the toxicity is not objectively gradable).

b. Serious Adverse Event (SAE)

A serious adverse event is any event that

- Resulting in death,
- Life-threatening,
- Leading to 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 above mentioned severity criteria (e.g. overdose, second cancers, pregnancies and new events may be considered as medically significant).

If a patient's partner declares a pregnancy, the sponsor must be informed without delay via the serious adverse event notification form (no severity criteria will then be checked).

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 is different 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, insufficient efficacy in life-threatening diseases, clinical data.

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 CTC-AE version 4.0 classification (see Appendix 6). 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 a doubt about the causal relationship between the event and the product under study (the relationship can then neither be formally excluded nor formally affirmed)

h. Responsibility of the promoter

Upon receipt of the investigator's report of the serious adverse event, the sponsor should issue an opinion on the causal relationship between the serious adverse event and the study product(s).
If the serious adverse event is related 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.

If it is a serious unexpected adverse reaction, or if it is a new fact, the sponsor writes an initial report which will be transmitted to the ANSM, the CPP and the EMA (via EudraVigilance) within 7 days in 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.

Events not to be considered serious

The progression of the disease as seen on imaging should not be considered as an SAE. On the other hand, events potentially linked to the progression but which may be secondary to the treatment should be reported (e.g. thromboembolic events, haemorrhagic phenomena, perforations, etc.)

Due to the severity of the disease in this study, certain conditions defined as SAEs 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

In this essay the reference documents will be:

- For aflibercept, the investigator brochure
- For 5-fluorouracil, the Summary of Product Characteristics for Fluorouracil Arrow® 50 mg (Appendix 8)
- For folinic acid, the Summary of Product Characteristics for Elvorine® (Appendix 8)

The versions of the PCRs used for the definition of expected or unexpected will be the latest available on the anniversary date of the start of the trial.

What to do

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.

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 (cf. appendix 9), documented as precisely as possible, dated and signed, within 24 working hours following the observation of the SAE, to the **FFCD's Randomization Management Analysis Center (CRGA) by fax (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 this follow-up beyond the trial patient's protocol follow-up period.

He/she transmits the additional information to the sponsor using an SAE reporting form (checking the Follow-up No. X box 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.

10. STATISTICAL ANALYSIS

The study is open-label, randomized (LV5FU2 alone versus LV5FU2 + aflibercept), non-comparative, and multi-center.

10.1 Provisional schedule of the study

The expected rate of inclusion is 5 patients per month.

First inclusion: January 2015
End of inclusions: January 2017
First analysis of the study: December 2017
Final analysis of the study: July 2018

10.2 Criteria of judgment

10.2.1 Primary efficacy endpoint

The primary endpoint of this trial is the rate of patients alive and progression-free within 6 months (+/- 15 days) after randomization. Progression will be assessed by the investigator according to RECIST 1.1 criteria based on imaging studies performed every 8 weeks, even in case of deferred treatments.
Clinical progressions, not confirmed on imaging, will not be counted in the primary endpoint.
Patients with progression on imaging studies prior to 6 months will be considered to be in progression at 6 months. Patients operated on their primary tumor before 6 months will be considered as non-progressive at 6 months.

A medical review will be carried out to decide on the case of each patient lost to follow-up or not evaluable at 6 months without identified progression before 6 months; in view of the patient's complete file, the patient may be considered as a treatment failure (progression), or as truly non-evaluable and not participating for the primary endpoint (a rate of 5% of additional patients has been planned for these situations).

10.2.2 Secondary criteria

- **The rates of patients alive and progression-free** according to the investigator will be evaluated at different time points: 6 months (primary endpoint) and 1 year.
    - **There are 2 definitions of progression depending on the investigator**: either radiological progression alone (at 1 year) or clinical and/or radiological progression (at 6 months and 1 year).
- **Progression-free survival**: Progression-free survival (median) may be estimated by the investigator. It will be defined as the time between the date of randomization and the date of the first radiological progression (RECIST 1.1 criteria) according to the investigator or death; patients alive without progression will be censored at the date of point or at the date of last informative examination if it is earlier.
- **Live and progression-free rates according to centralized review** (RECIST 1.1 criteria) will be estimated at 6 months and 1 year.
    - A centralized review of the imaging evaluations (CT or MRI with injection + chest CT) during the first 6 months will be performed. If centralized review is not possible for some CT scans, the response according to RECIST v1.1 criteria will be that estimated by the investigator.
- **Best response at 1 year**: evaluated from all radiological examinations of the patients according to the RECIST 1.1 criteria according to the investigator; it will be described by the rates according to the different categories: complete response, partial response, stability, progression or not evaluable
- **1-year and 3-year overall survival**: defined by the time from the date of randomization to the date of death; living patients will be censored at the earlier of the point or last date.
- **Tolerance**: evaluated by the toxicities observed and graded according to NCI-CTC v4.0; in particular, cutaneous toxicities of grade 2 or higher will be analyzed; the evolution of weight and WHO performance index will be described, as well as the SAEs. The time to onset of grade 3-4 toxicity will be studied.
- **Quality of life**: measured by the EORTC QLQ C30 questionnaire, completed at baseline and at each assessment visit during treatment, and at follow-up visits after cessation of treatment (every 3 months for 2 years and every 6 months for 1 year). Time to definitive deterioration of the QLQ-C30 global health score will be estimated; it is defined as the time from the date of randomization to the first date of a score decrease

of 5 points or more (from inclusion) without subsequent improvement of more than 5 points or death; living patients without deterioration of more than 5 points will be censored at the date of point or last quality of life assessment if earlier.

- **Resectability with curative intent at 1 year**: patients who have had their tumors (primary and/or secondary) resected after treatment (mentioning the R0, R1 or R2 character), after re-evaluation of their file in a multidisciplinary consultation meeting.
- **Prognostic character of thymidylate synthase polymorphisms** on the rate of patients alive and progression-free at 6 months across both arms.

10.3 Calculation of the number of subjects needed

In the FFCD 2000-05 study using LV5FU2 in the same indication, the median progression-free survival was 5.7 months.
The primary endpoint of the PRODIGE 25 study is progression-free survival within 6 months of randomization.
The assumptions for calculating the number of subjects required are:

- H_0 : A 6-month live progression-free rate of 40% or less is considered unattractive.
- H_1 : a rate of patients alive and progression-free at 6 months of more than 40% is necessary to consider the treatment interesting; a progression-free survival rate at 6 months of 60% is expected.

With a one-sided alpha risk of 5%, 56 evaluable patients in each arm (total 112 patients) would need to be included to achieve 90% power under the considered H1 hypothesis (calculations according to the exact binomial distribution)).
Taking into account a 5% rate of lost to follow-up**, 118 patients should be included**.

The decision rule is as follows:

- If 29 or more patients are alive and progression-free at 6 months, the efficacy of the treatment arm studied can be considered attractive.

This decision rule will only apply to the combination arm (LV5FU2 + Aflibercept). In the event that the trial continues into Phase III, the chemotherapy-only arm will be the control arm.

Depending on the number of patients actually lost to follow-up or deemed not evaluable, the decision rules for considering the treatment to be of value in terms of efficacy will be reviewed.

As an exploratory measure, the rates of patients alive and progression-free within 6 months will be compared between the two arms using a one-tailed Fisher exact test. This comparison will only be relevant in case of positive results; a negative result could in no case be interpreted as no difference between the two arms, for several reasons:

- the calculation of the number of patients was not done with a view to comparing the treatment arms; therefore, the power to show a difference is not sufficient;
- This study is a phase II study, and the assumptions used for the enrollment calculation are not yet precise enough to design a comparative study at this time;
- the H assumption$_0$ chosen does not represent the expected progression-free survival rate in the monotherapy arm, but the cut-off deemed necessary to consider an evaluation of the chemotherapy plus aflibercept arm in a legitimate phase III trial; thus, the difference between the H assumption$_0$ and the H assumption$_1$ is currently overestimated for a comparative study.

No interim analysis is planned. Nevertheless, the independent data review committee will be alerted in case of a significant number of AEs reported by the study pharmacovigilance.

10.4 Statistical analysis plan

10.4.1 Populations of analysis

ITT population: All patients included in the study regardless of inclusion and non-inclusion criteria and analyzed according to the treatment assigned by randomization

Modified ITT population (mITT): All patients in the ITT population with at least one assessment for the primary endpoint (imaging).

Per-Protocol (PP) population: All patients in the mTBI population:

- who have received at least 2 courses of chemotherapy at any dose (and 2 days of aflibercept in the corresponding arm),
- and whose WHO status at inclusion was ≤ 2

Tolerance Population: All patients included in the study who received at least one dose of treatment (regardless of dose and treatment). The analysis will be performed according to the actual treatment administered (presence or absence of at least 1 day of aflibercept administration).

The analysis of the primary and secondary efficacy endpoints will be performed in ITTm.

The primary endpoint and efficacy criteria will also be evaluated on the per-protocol population.

The safety analysis will be performed on the tolerance population.

10.4.2 Evaluation of the criteria

General considerations
All analyses will be performed using SAS software version 9.3 or higher or STATA V10 or higher. A statistical analysis plan will be written before the database is frozen. Any subsequent modification of this plan will have to be detailed, argued and commented in an updated version. These modifications may concern additional exploratory analyses not initially envisaged.

Continuous variables will be described using mean, standard deviation, median, interquartile range, minimum and maximum. Categorical variables will be described using frequencies and percentages. The 95% confidence intervals will be provided for the primary endpoint.

Evaluation of effectiveness criteria

The rate of patients alive and progression-free at 6 months will be calculated based on the investigator's assessment at 6 months +/- 15 days. It will be described using a percentage and a 95% confidence interval.

Survivals and times will be estimated by the Kaplan-Meier method. They 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 "reverse Kaplan-Meier" method.

The best response to treatment will be reported using percentages and numbers with their 95% confidence intervals.

Exploratory analysis of factors predictive of treatment response (progression vs. non-progression) will be performed by logistic regression; multivariate logistic regression will also consider treatment arm and stratification factors.

Evaluation of tolerance criteria

The number of cycles, dose received, and dose intensities will be described, as well as the percentage of patients who had a dose change or delay in administration with the related reasons.

The evolution of the WHO performance index and weight will be described.

The number of toxicities, by type and grade, will be reported over all treatment cycles. The percentage of patients with at least one grade 3-4 toxicity, at least one grade 5 toxicity, and those with maximum grade 1-2 toxicity will be calculated.

The time to grade 3-4 toxicity will be calculated by the Kaplan-Meier method.
The analysis of SAEs will be performed by the FFCD Pharmacovigilance Department. Quality of life will be assessed using the QLQ-C30 questionnaires.

Each score will be described at each measurement time by treatment arm (until one quarter of the baseline population is still followed). Means of change from inclusion to last assessment will be calculated in each arm. For the overall health score, a longitudinal analysis will be performed. The rate of patients with an improved score (increase of more than 5 points compared to inclusion), deteriorated score (decrease of at least 5 points (included)) and the rate of patients with a stabilized score at the last assessment will be reported using percentages and frequencies. An estimate of the time to deterioration of the quality of life score will be made using the Kaplan-Meier method.

10.5 Independent committee

An independent committee will be set up with an odd number of members including at least two physicians, a statistician and a pharmacovigilance expert. It will meet to rule on the safety data. It may also meet at any time during the trial when the Sponsor deems it useful.

11. BACKGROUND INFORMATION AND RATIONALE FOR THE STUDY

11.1 Colorectal cancers

11.1.1 Incidence

Colorectal cancers are the leading cancer incidence in France when both sexes are combined, with nearly 40,000 new cases in 2010 (1). Most of these cancers are diagnosed at the metastatic stage and it is estimated that about 50% become metastatic during their evolution. These cancers preferentially affect elderly subjects (median age 72 years for men, 75 years for women). Their incidence increases with age (2). Crude survival is 44%, relative survival 56% in France (3). In the 1990s, with the emergence of chemotherapy and improved postoperative survival, unadjusted survival increased from 54% to 57%.

11.1.2 Surgical treatment of metastatic colorectal cancer

Surgical removal is the only curative treatment. Thanks to advances in surgical techniques and anesthesia/resuscitation, an increasing number of patients can benefit from removal of the primary tumor and metastases. With the introduction of oxaliplatin and irinotecan in the therapeutic armamentarium, the resectability rate has increased but is known mainly from publications of series from specialized surgical centers (4) or on more or less selected patients from randomized studies. However, it seems certain that the use of certain chemotherapy combinations, in particular 5FU-oxaliplatin-irinotecan (FOLFOXIRI or FOLFIRINOX), is accompanied (5) by an increase in the resectability rate. Combinations of biochemotherapy (5FU and oxaliplatin or irinotecan) with an anti-VEGF antibody, bevacizumab (6), and with an anti-r EGF antibody,

cetuximab (7), also appear to increase the resectability rate of borderline metastases. Several ongoing randomized trials are exploring these avenues.

However, it has been shown (8) that the resection of all sites where metastases are initially located, especially in the liver, is essential, as their disappearance on current morphological examinations is not predictive of their definitive sterilization. For some patients with numerous metastatic sites in the liver segments and/or lung fields, there is therefore no hope of R0 secondary resection after aggressive chemotherapy.

Other patients cannot benefit from a resection of their primary tumor or their metastases because of their non-operability: old age, co-morbidities in particular cardiovascular.

11.1.3 Non-surgical treatment of unresectable or non-operable patients

11.1.3.1 Chemotherapy

For these two categories of patients, three well-conducted randomized studies (9-11) have shown that starting chemotherapy with a 5FU-based monotherapy does not affect the overall survival of patients provided that they switch to a combination of oxaliplatin or irinotecan in the second line. The convergence of these studies supports this statement with an excellent level of evidence. It appears, but these are only hypotheses from subgroup studies of two of these studies (MRC, FFCD), that impaired general status (WHO 2 and above) and/or the presence of more than one metastatic site are predictive of a survival advantage of the dual-therapy arms versus 5FU monotherapy. However, the differences are only statistically insignificant trends.

The search for factors predictive of the efficacy of dual therapy with oxaliplatin versus monotherapy led to the isolation of a thymidylate synthase (TS) genotype that, when present in the tumor host, is predictive of a better efficacy of this dual therapy (12): the progression-free survival benefit of first-line FOLFOX versus LV5FU2 was observed only in patients with a 5'UTR TS genotype of *2R/2R* (HR=0.39; 95% CI, 0.23-0.68) or *2R/3R* (HR=0.59; 95% CI, 0.42-0.82) respectively. Conversely, patients with *TS-5'UTR 3R/3R* genotype did not benefit from the addition of oxaliplatin (HR=0.96; 95% CI, 0.66-1.40). It is thus reasonable to think that the 3R3R genotype seems to be associated with an efficacy of 5-FU monotherapy as good as that of the FOLFOX combination. It is therefore interesting to validate this hypothesis by a prospective study stratifying patients on this criterion. If this genotype is predictive of the efficacy of 5-FU, this would also allow the two arms of a randomized study to be unbalanced on this criterion.

11.1.3.2 Targeted therapies (biotherapies)

Anti-angiogenic

Among recent studies, only one phase III study (13) evaluated the first-line combination of a targeted therapy (anti-VEGF antibody), bevacizumab, with 5FU (capecitabine) monotherapy. It showed a benefit on first-line progression, but no overall survival advantage for patients who received this anti-angiogenic therapy: the absence of bevacizumab in the first line was compensated by the administration of oxaliplatin, irinotecan or both in the second line or more in 68% of cases initially treated with capecitabine alone. The older Hurwitz study (14) with an obsolete comparator arm, IFL combination since discontinued, had shown a benefit in progression-free survival and overall survival (20.3 versus 15.6 months) but the subsequent lines of treatment, received by only 50% of patients, were not consistent with those that can be offered currently and did not include bevacizumab. The Kabbinavar trial (15), a combination of two cohorts of patients treated in two trials involving elderly subjects deemed unsuitable for irinotecan, shows an overall survival advantage for the arm treated with bevacizumab plus 5FU alone, but the subsequent lines received by patients are not well reported and the trial is also difficult to interpret. Therefore, it is not possible to recommend routine use of bevacizumab in the first line following these trials. In addition, the effect of this drug on overall survival has been proven in only two clinical trials. For other cancer sites, a larger number of phase III trials using bevacizumab have led to conflicting results that alter the certainty that this targeted therapy is unavoidable (16).

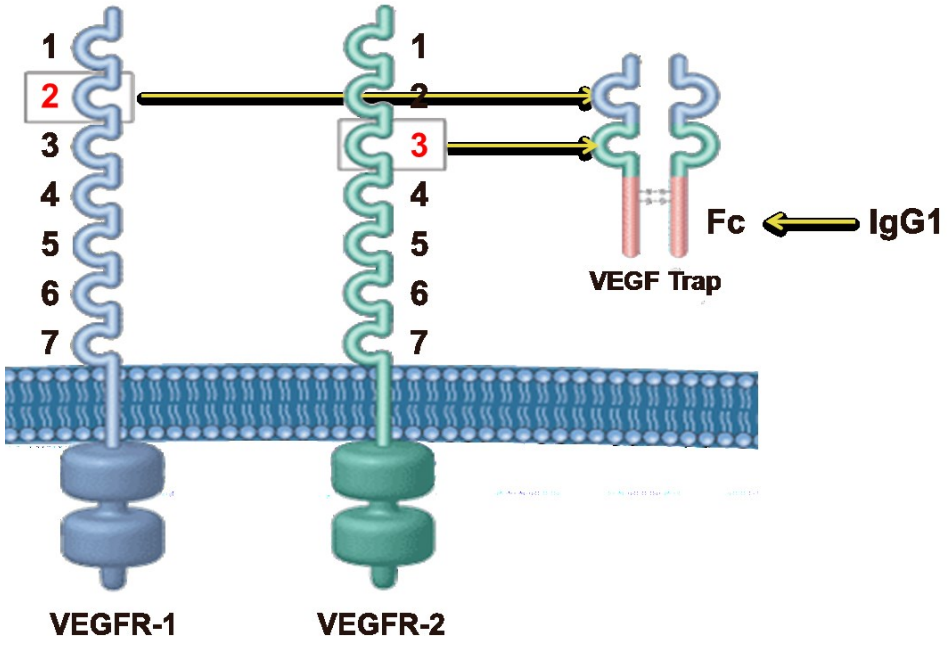
Two other multitargeted molecules with a predominantly anti-angiogenic focus, regorafenib (17) as a single agent and aflibercept in combination with 5FU and irinotecan in the VELOUR trial (FOLFIRI regimen) (18,19), have shown a significant effect on overall survival in second- or subsequent-line therapy

Aflibercept

This molecule is a recombinant fusion protein consisting of a fusion of the extracellular domain of the human vascular endothelial growth factor (VEGF) receptor with the Fc portion of human immunoglobulin G1 or IgG1 (Figure 1). Specifically, Aflibercept contains extracellular domain portions of two different vascular growth factors (VEGFRs): VEGFR1 (also described as Fit-1) and VEGFR2 (also described as KDR or Fik-1). Aflibercept is a drug presented as a sterile liquid for intravenous (IV) administration. It binds to VEGF in the picomolar range (pmol/L) and to placental growth factor (PIGF) with lower affinity. The affinity constants (KD) for binding to the two human VEGF isoforms, VEGF165 and VEGF121, are 0.50 pmol/L and 0.36 pmol/L, respectively. The KD for human PlGF2 is 39 pmol/L. The purpose of binding aflibercept to these ligands in vivo is to block angiogenesis and cell permeability, as aflipecept-bound VEGF can no longer interact with the endothelial wall. Aflibercept cannot mediate ADCC or CDC activity in endothelial and tumor cell lines.

Its activity has been studied in a broad pharmacological field against early and advanced solid tumors: sarcomas, ovarian, prostate, mammary, colon and gastric carcinomas, as a single agent or in combination with cytotoxic drugs. In a mouse model of ovarian and renal carcinomatous ascites, Aflibercept inhibited ascites formation and reduced tumor growth.

Figure 1 - Schematic representation of Aflibercept (VEGF Trap)



Two studies specifically examined serum Aflibercept levels in animal models by ELISA: free Aflibercept (not bound to VEGF) and bound Aflibercept (Aflibercept complexed to VEGF, 1:1 ratio). After IV administration in all animal species studied, free Aflibercept had a low clearance (0.5 to 3 mL/h/kg), a low volume of distribution (69 to 226 mL/kg), and a long apparent elimination half-life: T1/2 of 48 to 98 hours. Based on the correlation between exposure and activity in pre-clinical models, the proposed pharmacological target in humans for safe administration is such that excess free aflibercept is present.

The toxicity profile of aflibercept was evaluated in monkeys.

The main microscopic abnormalities were observed in the bone, nasal cavity, kidneys, ovaries and adrenals.

- Bones: thickening of the cortices and osteo-cartilaginous exostoses of the axial skeleton and extremities, correlated with a "pulled-in shoulder" attitude on clinical examination.
- Nasal cavity: degeneration/regeneration of respiratory and olfactory epithelium, atrophy/loss of nasal septum and/or turbinates, often associated with hemorrhages and superinfected exudates.

- Kidneys: increased glomerular mesangial matrix, associated in some individuals with hypoprotidemia, hypoalbuminemia, elevated BUN, proteinuria and/or microalbuminuria.
- Ovaries: decrease in the number of mature follicles, granular and/or thecal cells associated with inhibition of reproductive function.
- Adrenals: decreased vacuolization in the adrenergic fascicle zone and cytoplasmic eosinophilia.

In addition, focal proliferation/degeneration abnormalities were observed in several organs, particularly the digestive tract, bladder, heart and brain of some monkeys. Elevated liver enzymes were noted in some individuals, associated with portal inflammation and necrosis. Administration of aflibercept resulted in decreased sperm motility and an increased rate of morphologically abnormal sperm.

Most of these abnormalities associated with aflibercept administration occurred at the lowest doses tested (1.5 to 3 mg/kg/dose).

With the exception of bone and nasal abnormalities, aflibercept-induced changes resolved within 5 months of discontinuation.

Aflibercept did not induce a frequent immune response in monkeys treated for 3 months by SC or IV, with an increased incidence of an antigenic response when treated for 6 months.

In male mice, 3 months of subcutaneous administration induced a significant reduction in microvessel density mainly in the liver, pancreatic islets, thyroid follicles at all doses, and less markedly in the pituitary and adipose tissue. Single administration in rodents induced a moderate, prolonged and reversible elevation of systolic and diastolic blood pressure. The induced hypertension in rats was sensitive to several classes of antihypertensive drugs, such as angiotensin-converting enzyme inhibitors, calcium channel blockers, adrenergic receptor antagonists, and NO modulators.

In rabbits, aflibercept moderately delayed parietal repair and wound healing as early as 0.3mg/kg/administration.

As of 01/31/2010, aflibercept has been administered to more than 3100 patients included in trials involving solid cancer tumors, 76 healthy subjects, 41 patients with ophthalmic disease, at doses up to 800 µg/kg SC twice weekly, 7 mg/kg IV every 2 weeks and 9 mg/kg IV every 3 weeks. The most frequently reported unexpected side effects when prescribed as monotherapy were fatigue, hypertension, headache, nausea, abdominal pain, dysphonia, diffuse musculoskeletal, extremity, and lumbar pain, anorexia, vomiting, hemorrhage (mainly epistaxis), constipation, diarrhea, respiratory abnormalities (mainly dyspnea), arthralgias, edema, proteinuria, cough, fever, myalgias, and weight loss. The toxicities described in the phase III VELOUR study in combination with FOLFIRI chemotherapy (5FU, folinic acid, irinotecan) are given in Tables 1 and 2. In this study, performed as a second-line treatment in a patient population similar to this new study, the toxicity profile of aflibercept was considered acceptable and predictable within the known complications of anti-angiogenic agents. Adding aflibercept to biochemotherapy with 5FU and irinotecan resulted in an increase in the specific toxicity of this chemotherapy, in particular the rate of neutropenia, diarrhea and stomatitis.

Pharmacologic target was achieved at a dose ≥2 mg/kg IV every 2 weeks. Free aflibercept remained in excess of bound aflibercept over interval dosing at this dose and above. Tumor responses and stabilizations (>1 year) were observed at dose levels ≥800 µg/kg SC and ≥1 mg/kg IV for aflibercept alone and in combination with cytotoxic drugs.

Its activity on tumor growth was similar to that obtained with monotherapy when combinations with paclitaxel, docetaxel, or irradiation were used in animal models, and was synergistic with 5-fluorouracil (5-FU), and irinotecan.

Table 1. Most frequent adverse events in the phase III VELOUR trial (excluding events in the anti-angiogenic class)

Population evaluated for toxicity of patients	**Placebo, N = 605**	**Aflibercept N = 611**

	All grades	Grade 3-4	All grades	Grade 3-4
Diarrhea	56.5	7.8	69.2	19.3
Neutropenia	56.3	29.5	67.8	36.7
Complicated neutropenia	-	2.8	-	5.7
Asthenia	50.2	10.6	60.4	16.9
Stomatitis & ulcerations	34.9	5.0	54.8	13.7
Thrombocytopenia	33.8	1.7	47.4	3.3
Infections	32.7	6.9	46.2	12.3
Anorexia	23.8	1.8	31.9	3.4
Weight loss	14.4	0.8	31.9	2.6
Erythro-dysesthesia palmo-plantar	4.3	0.5	11.0	2.8
Skin hyperpigmentation	2.8	0	8.2	0
Dehydration	3.0	1.3	9.0	4.3

Van Cutsem E et al, ESMO WCGI 2011

Table 2. Adverse events considered to be associated with Anti-VEGF activity in the phase III VELOUR trial (total population)

Population evaluated for toxicity of patients	**Placebo/FOLFIRI, N=605**		**Aflibercept/FOLFIRI, N=611**	
	All grades	Grade 3/4	All grades	Grade 3/4
Proteinuria	40.7	1.2	62.2	7.9
Hypertension	10.7	1.5	41.4	19.3
Hemorrhage	19.0	1.7	37.8	2.9
of intestinal origin	5.1	1.0	10.0	2.0
Dysphonia	3.3	0	25.4	0.5
Headaches	8.8	0.3	22.3	1.6
Venous thromboembolic events	7.3	6.3	9.3	7.9
Thromboembolic event Arterial	1.5	0.5	2.6	1.8
Fistula	0.5	0.2	1.5	0.3
Delayed healing	0.8	0	0.5	0.3
Intestinal perforation	0.5	0.3	0.5	0.5

Van Cutsem E et al, ESMO WCGI 2011

Complete information regarding aflibercept will be provided to the trial investigators.

Anti-EGFr (epidermal growth factor receptor)

A large international multicenter study, the Cristal trial, showed that the combination of weekly cetuximab with the FOLFIRI regimen in the first line of treatment gave patients receiving it a progression-free survival and overall survival advantage (20), provided that their tumor did not have a K-RAS mutation. A difference in progression-free survival had already been shown in second-line treatment after failure of 5FU- and irinotecan-based chemotherapy in a phase II study (21). For some, it seems more interesting to place this treatment later in the management of patients. A strategy study evaluating these two types of therapeutic sequences would be useful.

The cetuximab-oxaliplatin combination has also been evaluated in first-line therapy in combination with 5FU. In the OPUS trial (22), the cetuximab-FOLFOX combination provided a progression-free survival benefit. In combination with the Xelox (xeloda-oxaliplatin) regimen, cetuximab did not provide an overall survival benefit (23). The addition of the skin toxicities of this oral 5FU and cetuximab is thought to have induced a decrease in the dose-intensity of cytotoxic treatment, explaining this negative result.

The combination of cetuximab and 5FU has not been evaluated to date.

11.2 Rationale for the study

The combination of aflibercept and 5FU alone has not been evaluated to date.
Aflibercept at a dose of 4 mg/kg has already been used in combination with 5FU at the doses used in the simplified LV5FU2 regimen (folinic acid 400 mg/m^2 IV over 90 min, followed by 5FU 400 mg/m^2 as an IV bolus at D1, followed by a continuous infusion of 5FU 2400 mg/m^2 over 46 h) (23) in the above-mentioned VELOUR trial, evaluating its combination with FOLFIRI (= simplified LV5FU2 + irinotecan). This study was preceded by a phase I trial validating the doses used (24). There is therefore no need for a phase I study if the same doses of 5FU are used, without irinotecan, as part of a strategy to de-escalate toxicity in patients to be managed over a long period of time, and not to find the maximum tolerable dose of the combination.

The aflibercept-LV5FU2 combination may be of interest in patients who will never be resectable or operable and in whom 5-FU monotherapy may be proposed to delay the toxicities of chemotherapy combinations. In this setting, it is possible that aflibercept may provide a survival advantage. The preliminary VELOUR study (18) does not suggest that toxicity will have a significant impact on quality of life and suggests that progression-free survival will be prolonged in the aflibercept arm.

This is what the FFCD 11-01 study, PRODIGE 25, proposes to study as a preliminary to strategic studies evaluating the usefulness of using targeted therapies from the first line.

This study will evaluate both the efficacy of the combination and its tolerance, through the study of toxicities and quality of life. Quality of life will be studied through the EORTC QLQC30 questionnaire.

The 2R2R-2R3R versus 3R3R polymorphism of thymidylate synthase seems to predict better efficacy of 5FU monotherapy. Stratification on this criterion will allow to confirm or not the prognostic or predictive character of the efficacy of 5FU associated with these polymorphisms.

The project of this study was studied and validated by the scientific council of the French-speaking Federation of Digestive Oncology (FFCD) then by the Digestive Group of UNICANCER within the framework of their Partnership for Research in DIGEstive Oncology (PRODIGE).

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13. CONSIDERATIONS

14. ADMINISTRATIVE

STUDY SPONSOR

The sponsor of the study is the Fédération Francophone de Cancérologie Digestive (FFCD). The study was registered under the number EudraCT 2014-001837-10.

REMINDER OF THE TEXTS IN FORCE

This test will be carried out according to the new European Directive 2001/20/EC.

LIABILITY INSURANCE

Insurance was taken out by the sponsor on 12/05/2014 under number 137681, in accordance with Article L 1121-10 of the Public Health Code (Appendix 11).

REQUEST FOR AUTHORIZATION TO THE CPP AND ANSM

This protocol received the favorable opinion of the CPP (Committee for the Protection of Persons) OUEST I of Tours on xx/xx/2014 (Appendix 12).
This protocol received authorization from the ANSM (Agence Nationale de Sécurité du médicament et des produits de santé) on xx/xx/2014 (Appendix 13).

COLLECTION OF THE PATIENT'S CONSENT

The investigator undertakes to obtain the patient's written clinical and biological consents (information sheets and consent forms in Appendix 1 and 2) before the patient is included in the study. A copy of these consents must be kept by the investigator for 15 years, to be presented to the regulatory authorities in case of inspection. The original must be given to the patient.

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 data bank of the Center of Randomization and Management Analysis of the FFCD, with the exception of the elements relating to the identity of the patients.

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 trial may be consulted by a person mandated by the FFCD and/or by the health authorities to conduct an audit. On-site visits to the files, scheduled after agreement by the investigator, may take place during or after the period of inclusion in the trial This protocol will be monitored by the FFCD's mobile ARCs.

15. PUBLICATION RULES

They will be in accordance with those established in the framework of the PRODIGE Partnership (Annex 10)