FFCD 1302

EFFICACY AND SAFETY OF AFLIBERCEPT IN COMBINATION WITH FOLFIRI CHEMOTHERAPY AS FIRST-LINE TREATMENT IN PATIENTS WITH METASTATIC COLORECTAL

Phase II single-arm multicenter

EudraCT n° 2013-004081-33

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TABLE OF CONTENTS

1. STUDY OBJECTIVE 4

1.1 Objectif principal 4

1.2 Objectifs secondaires 4

1.3 Exploratory study 4

2. PATIENTS SELECTION 4

2.1 Inclusion criteria 4

2.2 Non inclusion criteria 5

3. INCLUSION ASSESSMENT 5

4. INCLUSION 6

5. STUDY SCHEMA 7

6. TREATMENT 7

6.1 Aflibercept administration 8

6.2 FOLFIRI Administration 8

6.3 Tretament modifications in case of toxicity 8

6.3.1 Aflibercept 8

6.3.2 FOLFIRI 10

6.3.3 Criteria for Stopping Chemotherapy and/or Aflibercept 12

6.3.4 Concomitant treatments 13

6.4 Contraindicated treatments 13

7. PATIENTS MONITORING 14

7.1 During the treatment 14

7.2 After discontinuation of the treatment for other reason than progression 15

7.3 After the treatment discontinuation for progression 15

8. LOGISTIC FOR ANCILLARY STUDY 15

9. SERIOUS ADVERSE EVENTS (SAE) 16

10. STATISTICAL ANALYSIS 18

10.1 Judgement endpoint 19

10.1.1 Main efficacy criteria 19

10.1.2 Secondary criteria 19

10.2 Sample size calculation 20

10.3 Statistical analysis plan 20

10.4 Independant commitee 21

10.5 Imaging Review Committee/Radiology Panel 21

10.6 Steering committee 21

10.7 Biological committee 21

11. BACKGROUND INFORMATION AND RATIONALE FOR THE STUDY 21

12. BIBLIOGRAPHY 24

13. ADMINISTRATIVE CONSIDERATIONS 26

REVIEW AND FOLLOW-UP SCHEDULE

	Before Treatment	During Treatment and in case of treatment stop without porgression			After Treatment stop after progression
	Within 3 weeks before inclusion	Before each cycle	Every 8 weeks	End of treatment examination (30 days after last administration)	Every 3 months during 2 years and every 6 months until death
Clinical and bioogical consent	X				
Clinical Examination					
Weight, Height, Blood pressure	X	X	X	X	X
OMS General Status	X	X	X	X	X
Toxicities NCI-CTCAE version 4.0	X****	X	X	X	X
MORPHOLOGICAL EXAMINATION* **					
Spiral thoraco-abdomino-pelvic CT scan (TDM-TAP), with and without injection of contrast agent, performed at most 3 weeks before inclusion. In case of contraindication to iodinated contrast injection, a hepatic or abdominal MRI with gadolinium injection and a thoracic scanner without injection may be performed	X		X		X
BIOLOGICAL EXAMININATION					
Biology	X*	X**	X*	X**	X**
Pregnancy test for women in period of genital activity (within 7 days prior to inclusion)	X				
CEA	X		X		
ANCILLARY STUDY					
3 heparinized blood tubes of 10 mL	X (Before 1st cycle)	Before the 3rd cycle (D28 before administration)			
Biopsies, ou bloc de tumeur, fixées en paraffine	X				

1. Study Objective

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

1.1 Objectif principal

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

1.2 Objectifs secondaires

The secondary objectives of the study are :

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

1.3 Exploratory study

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

2. Patients selection

2.1 Inclusion criteria

- Age ≥ 18 years old
- General Status WHO ≤ 2
- Adenocarcinoma of the rectum or metastatic colon histologically proven or on primary tumor or metastasis
- Non-resectable metastasis(s) and/or non-operable patient
- At least one measurable target according to RECIST version 1.1 criteria, not previously irradiated

- Lack of prior treatment for metastatic disease. Previous adjuvant chemotherapy completed 6 months or more prior to the diagnosis of metastasis is permitted.

- Adequate bioassay: Hb ≥ 9 g/dl, neutrophils ≥ 1500 /mm3 , platelets ≥ 100 000/mm3 , total bilirubin ≤ 1.5 x ULN, creatinine clearance > 50 mL/min (Cockroft and Gault formula), PAL < 5 x ULN, ASAT and ALAT ≤ 5 x ULN, GGT < 5 x ULN,

- Proteinuria on urine strip < 2+. If ≥ 2+ do 24 hrs proteinuria which must be ≤ 1 g

- Patient who signed the informed consent

2.2 Non inclusion criteria

- Patients with clinical symptoms (occlusion, hemorrhage)

- Presence of brain metastases, uncontrolled spinal cord compression, carcinomatous meningitis, signs of brain or leptomeningeal damage.

- Gilbert's disease

- Uncontrolled hypercalcemia

- Uncontrolled hypertension (PAS > 150 mmHg and PAD > 100 mmHg) or history of hypertensive crisis or hypertensive encephalopathy

- Any progressive disease that has not been balanced in the last 6 months: hepatic insufficiency, renal insufficiency, respiratory insufficiency.

- Myocardial infarction, severe/unstable angina pectoris, coronary artery bypass grafting, NYHA class III or IV congestive heart failure, stroke or transient ischemic attack within 6 months prior to inclusion.

- Gastrointestinal bleeding/hemorrhage grade 3 or 4, treatment-resistant peptic ulcer, erosive esophagitis or gastritis, infectious or inflammatory bowel disease, diverticulitis, pulmonary embolism or other uncontrolled thromboembolic event, unhealed bone fractures in the 3 months prior to inclusion

- Major surgery within 28 days prior to the start of treatment

- Known acquired immunodeficiency syndrome (AIDS-related illnesses) or known HIV infection requiring antiretroviral treatment

- Treatment with CYP3A4 inducers, unless stopped for more than 7 days

- History of haemopathic malignancy or cancer (except those treated for more than 5 years and considered cured), carcinoma in situ of the uterine cervix and skin cancer treated (melanoma excluded)

- Lack of effective contraception in patients (male and/or female) of childbearing age, pregnant or breastfeeding women, women of childbearing age who have not had a pregnancy test.

- Any contraindications to the drugs used in the study

- Impossibility to undergo the medical follow-up of the trial for geographical, social or psychological reasons.

- Patients on newer oral anticoagulants (such as rivaroxaban XARELTO® , apixaban ELIQUIS® , dabigatran PRADAXA®) unless relayed by VKA

3. INCLUSION ASSESSMENT

The inclusion assessment must be completed within 3 weeks prior to inclusion and includes:

<u>Full clinical examination :</u>

- - Weight, height, body surface area
- - Blood pressure (SBP and DBP)
- - General status WHO
- - Search for pre-existing symptoms at inclusion

Biological assessment :
- - Hemoglobin (hemoglobin, PNN, platelets), creatinine, blood ionogram, magnesemia, serum calcium, PT, albuminemia, total, free and conjugated bilirubinemia, transaminases, alkaline phosphatases, LDH, proteinuria (urine test strip) and 24-hour proteinuria if test strip > 2+, INR for patients on VKA.
- - Marker: ACE
- - Pregnancy test for women in period of genital activity (within 7 days prior to inclusion)
- - Specimen for the biological ancillary study if the patient has signed the biological consent form.

Morphological evaluation of the tumor :
- - Spiral thoraco-abdomino-pelvic CT scan (TDM-TAP), with and without injection of contrast agent, performed at most 3 weeks before inclusion.
- In case of contraindication to iodinated contrast injection, a hepatic or abdominal MRI with gadolinium injection and a thoracic scanner without injection may be performed.
- Morphological examinations should be the same throughout the follow-up of the patient.
- Make a copy of the images which will be sent to the CRGA of the FFCD for centralized proofreading.

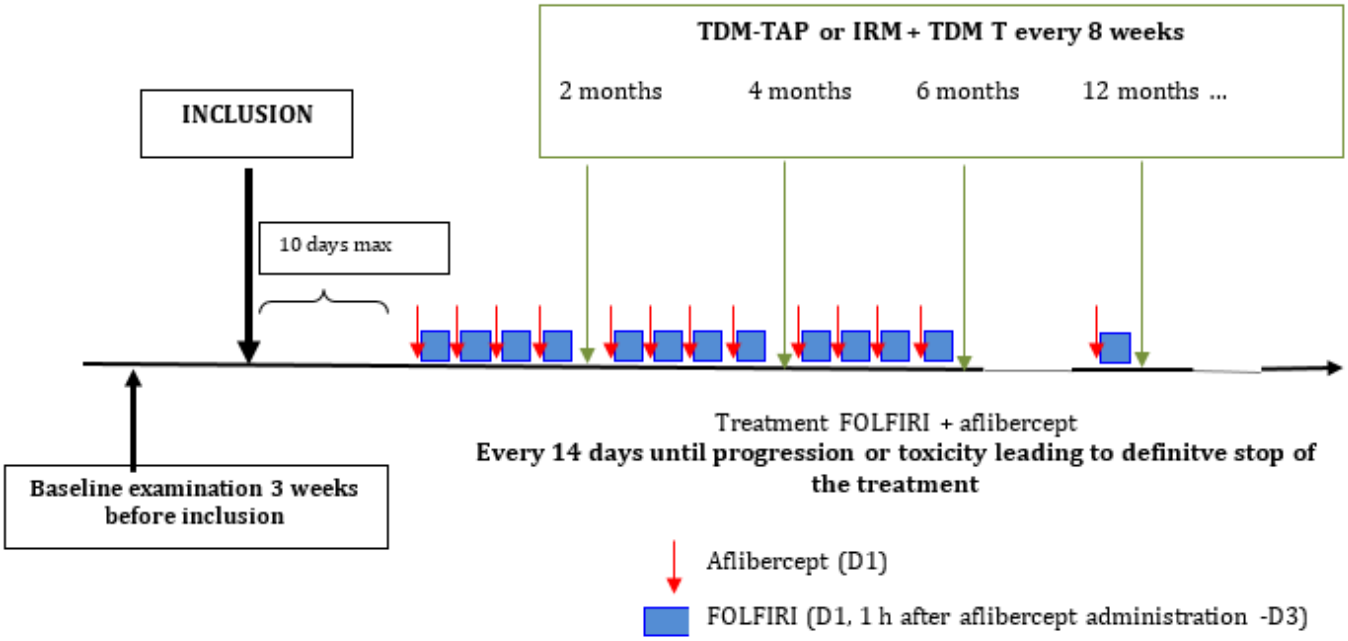
Ancillary biological study on the prognostic value of Treg lymphocytes, monocytes, dendritic cells, pro-angiogenic factors (cf chapter 8), PlGF :
- - 3 heparinized blood tubes of 10 mL (supplied by the Promoter)
  - before the first treatment (inclusion assessment or day of the first treatment before administration of the treatment)
  - before the 3rd cure (D28 before administration of the treatment)

- Kerosene biopsies or tumor blocks for immunohistochemistry (PlGF) (prior to treatment administration).

4. INCLUSION

The inclusion will be made by the CRGA of the FFCD after receipt of the fax of inclusion (form 1 of the observation book) at 03 80 38 18 41. The CRGA is open from Monday to Friday from 9am to 6pm.
A confirmation of inclusion will be faxed back to the investigator.
After inclusion of the patient in the study, treatment should begin within 10 days.
An observation notebook will be sent at the opening of the center. A new observation notebook will then be sent after each inclusion.
The first inclusion in a center will trigger the sending of the aflibercept treatment. The management of the aflibercept stock for the subsequent inclusions will be done by the pharmacy of the center. The treatment will be sent by LC2, the company responsible for the distribution.

5. STUDY SCHEMA

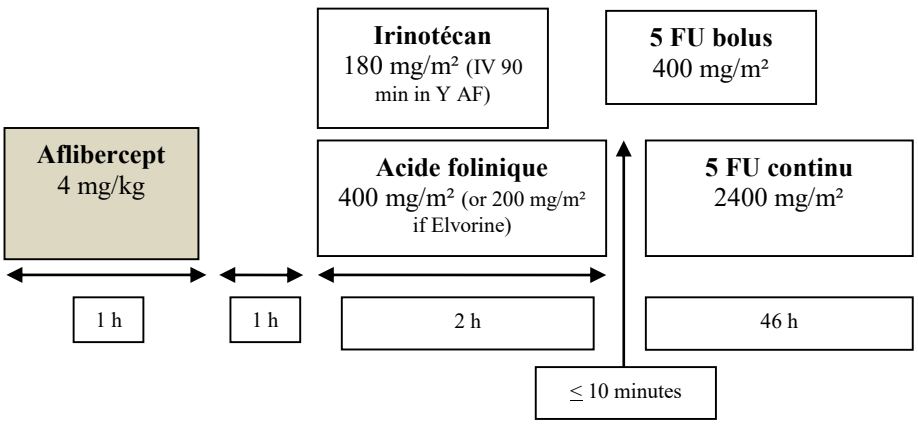


6. TREATMENT

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

Aflibercept will be provided free of charge by Sanofi as part of the study, and will be distributed by LC2.

Product traceability will be ensured by pharmacies.



6.1 Aflibercept administration

Aflibercept [25 mg/mL IV infusion solution - 8 mL vials (200 mg/vial)] should be administered at the start of each chemotherapy course. The vials should be stored in the original package in a refrigerator at 2-8°C and protected from light.
Aflibercept should be administered at 4 mg/kg and should be diluted directly in the infusion bag with 0.9% sterile sodium chloride or G5%. Diluted solutions should be administered using infusion sets with a 0.2 micron polyether sulfone filter. Infusion sets should be made of one of the following materials: polyvinyl chloride (PVC) containing bis(2-ethylhexyl) phthalate (DEHP), non-DEHP PVC containing trioctyl trimellitate (TOTM), polypropylene, PVC coated internally with polyethylene or polyurethane. Please note: Polyvinylidene fluoride (PVDF) or nylon filters should not be used.
The solution must be prepared in a sterile environment.
Aflibercept will be administered within 1 hour. The preparation should not exceed 2 hours at room temperature (25°C).

6.2 FOLFIRI Administration

Irotecan will be administered IV at a dose of 180 mg/m² as a 90-minute infusion and folinic acid Y infusion.
Folinic acid will be administered IV at a dose of 400 mg/m² (or 200 mg/m² if Elvorine) as a 2-hour infusion in 250 mL of G5%.
The 5 FU bolus will be administered in less than 10 minutes at 400 mg/m² in 100 mL of G5%.
The continuous 5 FU will be administered IV at a dose of 2400 mg/m² over 46 hours in G5% (qsp 230 mL, 5 mL/h).

6.3 Tretament modifications in case of toxicity

6.3.1 Aflibercept

In the case of aflibercept toxicity, dose adjustments should be made based on the highest observed toxicity grade on the NCI-CTCAE version 4.0 scale (Appendix 6).

If the patient has multiple toxicities, dose titration should be based on the highest toxicity.
Once the dose is decreased, no dose increase is permitted.
Aflibercept will be administered if PNN > 1500/mm3 and platelets > 100,000/mm3 and after recovery to a grade < 1 for any other toxicity (except alopecia). In febrile neutropenia or neutropenic sepsis: In the event of recurrence after decreasing the dose of irinotecan and 5FU, consideration may be given to reducing the dose of aflibercept to 2 mg/kg (see Product recommendations).

Toxicity	Grade (NCI-CTCAE version 4.0)	Action
Hypertension	**Grade ≤ 2**	Start or modify antihypertensive treatment if necessary. No dose modification, no postponement of treatment.
	Grade 3 (nécessitant plus d'un traitement antihypertenseur ou nécessitant d'intensifier le traitement antihypertenseur)	• Postpone administration of FOLFIRI and aflibercept (maximum 2 weeks) until recovery of BP (blood pressure) < 140/90 or to a MAP < 160 if MAP < 90 for patients with a known history of isolated systolic hypertension : o - If BP is controlled within 2 weeks of postponement • 1st event: Re-administer FOLFIRI and aflibercept at the same dose. • 2nd Episode: Re-administer FOLFIRI at the same dose and re-administer aflibercept at 2 mg/kg

		• 3rd event: definitive stop of aflibercept, resumption of FOLFIRI • - If after 2 weeks of delay, BP is still not controlled despite antihypertensive treatment: resume FOLFIRI at the same dose and stop aflibercept for one cycle of FOLFIRI (14 days). Re-evaluate BP at the next cycle and restart aflibercept at 2 mg/kg if BP is controlled. • If Grade 3 recurs despite optimal antihypertensive therapy and dose reduction of aflibercept, or if BP is still not controlled despite a 2-week delay of aflibercept (4 weeks after last administration): DEFINITIVE STOP of aflibercept. FOLFIRI 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 discontinuation of aflibercept and Cardiac Advice
Arterial thromboembolic event	Whatever the grade is	DEFINITIVE discontinuation of aflibercept
Venous thromboembolic event	**Grade 3**	Episode 1: Heparin therapy and continuation of ablibercept1 2nd episode despite appropriate anticoagulant treatment: DEFINITIVE STOPPING of aflibercept
	Grade 4	DEFINITIVE STOPPING of aflibercept
Haemorraghe	**Grade 3-4**	DEFINITIVE STOPPING of aflibercept
Intestinal Perforation i/ intestinal fistul	Whatever the grade is	DEFINITIVE STOPPING of aflibercept
Posterior Leucoencephalopathy postérieure	Whatever the grade is	DEFINITIVE STOPPING of aflibercept

Proteinuria

A urine test strip should be performed before each administration of aflibercept (proteins, red blood cells, leukocytes):

- If proteinuria is < 2+ and there is no hematuria, aflibercept may be administered

- If proteinuria is > 2+, do not administer aflibercept and reinstate it as soon as 24-hour proteinuria is < 2 g. If proteinuria > 2 g/24 reappears, aflibercept should be suspended until 24-hour proteinuria < 2 g and reintroduced at 2 mg/kg

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

Hypersensibility reaction to aflibercept

Symptom severity	Recommandation
Light and moderate **Example: Grade < 2: skin reaction, pruritus, flush, rash, dyspnea, tachycardia, hypotension, anxiety, headache, myalgia, edema, nausea**	SUSPEND the aflibercept infusion - Administer diphenydramine 50 mg IV and/or dexamethasone 10 mg IV - Resume aflibercept infusion after recovery
Severe **Example: symptomatic bronchospasm, generalized urticaria, SBP < 80 mmHg, angioedema, anaphylaxis**	STOP the aflibercept infusion. - Administer diphenydramine 50 mg IV and/or dexamethasone 10 mg IV and/or epinephrine if necessary - DEFINITIVE STOP of aflibercept

Non-healed 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 (e.g., chamber placement, biopsies, tooth extraction), aflibercept can be reintroduced as soon as healing is complete.

Aflibercept should be permanently discontinued if there is an open wound or a non-healing wound requiring medical intervention.

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6.3.2 FOLFIRI

Before each treatment we will check: blood count, creatinine, proteinuria (urine test strip) and 24-hour proteinuria if test strip > 2+. Chemotherapy will be started if :

- PNN 1,500/mm3

- 100,000/mm3 wafers

- Hemoglobin 9 g

The chemotherapy cure will be delayed by one week: in case of moderate hematological toxicity (PNN < 1,500/mm3 and/or platelets < 100,000/mm3), persistent digestive toxicity (oral ulcerations, diarrhea, or grade 3-4 esophagitis). The dose of 5FU will then be modified according to the instructions in Tables 1 and 2.

If creatinine levels are elevated, further investigations will be carried out by the investigator who will judge whether additional therapeutic measures should be taken or whether progression under treatment should be diagnosed.

Chemotherapy toxicities are assessed using the NCI-CTCAE version 4.0 scale.

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Table 1 : Adaptation of the dose of FOLFIRI according to the maximum toxicity on the day of the treatment or in between treatments.

Grade (NCI-CTCAE version 4.0)	5Fluorouracile	Irinotécan
Neutropenia, thrombopenia		
Grade 2	- 50% reduction of the bolus	- No change
Grade 3	- Elimination of the bolus, 25% reduction of the continuous 5FU	- No change
Grade 4	- Elimination of the bolus, 25% reduction of the continuous 5FU	- 25% discount
Febrile neutropenia		
Grade 3	Elimination of the bolus + G-CSF and if reccurence then definitive stop	
Grade 4	Adaptation according neutropenia grade	
Diarrhea despite a treatment		
Grade 2	- 50% reduction of the bolus	
Grade 3	- 50% bolus reduction, 25% continuous 5FU reduction	- 25% discount - 25% discount %
Grade 4	- Stop Chemotherapy	- Stop Chemotherapy
Mucitis		
Grade 2	- 50% reduction of the bolus	- No modification
Grade 3	- Stop bolus, reduction de 25% of 5FU continu	- No modification
Grade 4	- Stop Chemotherapy	- Stop Chemotherapy
Vomiting		
Grade 3	- No modification	- Réduction de 25 %
Grade 4	- Stop Chemotherapy	- Stop Chemotherapy
Hand-foot syndrome		
Grade 2	- 25 % reduction of 5FU continu	- No modification
Grade 3	- 50% reduction of the bolus, 50% reduction of the 5FU continu	- No modification
Toxicité non hématologique en dehors de l'alopécie		
Grade 3	- 25 % reduction of 5FU continu and of the bolus	- 25% discount - Stop Chemotherapy
Grade 4	- Stop Chemotherapy	

Table 2 : Adaptation of the doses of 5-FU and irinotecan after a 2nd episode of toxicity, after a 1st dose reduction and a further postponement of one week.

TOXICITY	5-FU	Irinotécan
PNN ≥ 1400, platelets ≥ 90 000	No bolus	No modification
1000 ≤ PNN < 1400 and/or 75 000 ≤ platelets < 90 000	No bolus and 75 % of continous IV	Reduction of 25 %
Persisting digestive tox* of grade 1 or 2 isolated	50 % of continous IV	Reduction of 25 %
PNN < 1000 and/or platelets < 75000 and/or persisting digestive toxicity* grade 3-4	No 5FU and postponed of 8 days	No irinotecan
Grade 4 febile neutropenia, grade 4 neutropenia (PNN < 500), thrombopenia 3-4 (<50000) and/or digestive toxicity* grade 3-4	No bolus and 50 % of continous IV	Reduction of 40 %

No modification of folinic acid.

6.3.3 Criteria for Stopping Chemotherapy and/or Aflibercept

- Major toxicity requiring the definitive cessation of treatment:

If aflibercept toxicity requires discontinuation for 4 or more consecutive weeks (i.e., a margin of 2 days for each 7-day delay 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 the event of discontinuation of aflibercept due to an intercurrent event (radiotherapy, hospitalization for reasons other than toxicity, etc.), the investigator will decide whether or not to restart aflibercept. The treatment will then be collected as part of the study (in the CRF).
  - Aflibercept can be stopped immediately and permanently at the investigator's sole discretion, if the investigator considers it necessary for the patient.
- If aflibercept is delayed or discontinued, concomitant chemotherapy (FOLFIRI) may be continued as described in this protocol.
- If FOLFIRI is discontinued, aflibercept will be stopped (no monotherapy administration).
- If chemotherapy is postponed for one to three weeks, aflibercept will also be postponed and will be resumed at the same time as the chemotherapy according to the protocol. Chemotherapy toxicity assessment for deferral should be done weekly to avoid unnecessary delays in resumption.
- Chemotherapy may be stopped if the patient refuses to continue at his or her request or withdraws consent (to be documented).

- A patient will stop chemotherapy following a life-threatening toxic reaction in the opinion of the patient's physician.
- Progressive illness.

Patients will be monitored until death and types of treatment will be collected after progression under the first line of treatment.

6.3.4 Concomitant treatments

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

Primary prevention of chemo-induced nausea and vomiting (AFSOS recommendations) :

On D1 of chemotherapy

- anti-5HT3: Odansetron (Zophren) IV 8 to 16 mg; 30 minutes before,

- Aprepitant (Emend): per os, 125 mg, 1 hour before,

- Dexamethasone: IV 8 to 16 mg or methylprednisolone hemisuccinate 80 mg IV.

After chemotherapy

- Aprepitant per os: 80 mg in the morning of D2 and D3.

Primary prevention of mucites (AFSOS recommendations) :

Prescriptions of mouthwashes :

- Sodium bicarbonate 1.4% pure, without addition of any other product. As often as possible, minimum 8 to 10 times a day, in gargle and at a distance from meals. Oral hygiene advice (soft toothbrush).

Primary prevention of diarrhea :

- Hygieno-dietary rules: diet low in residues and good oral hydration.

- In case of acute non-febrile diarrhea: loperamide 4 mg then 2 mg/2 h during at least 12 h after the last liquid stool, without exceeding 48 h.

Atropine, 0.25 mg SC is authorized before the infusion of irinotecan, for the prevention of acute cholinergic syndrome.

In case of anemia, it will be treated according to its mechanism: spoliation, inflammatory or by spinal cord insufficiency.

The subcutaneous administration of growth factor is authorized:

- as a curative treatment for 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 Grade 3-4 concurrent neutropenia, Grade 4 neutropenia > 7 days. A growth factor will be used for all subsequent cycles.

6.4 Contraindicated treatments

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

7. PATIENTS MONITORING

7.1 During the treatment

- **Before each chemotherapy treatment :**
    - Clinical examination: weight, body surface area, WHO general condition, blood pressure
    - Biological assessment: CBC, platelets, creatinine, proteinuria (urine test strip) and 24-hour proteinuria if test strip > 2+, INR strongly recommended for patients on VKA.
    - Toxicity evaluation according to NCI-CTCAE version 4.0

For patients participating in the ancillary biological study :

- Sampling of 3 heparinized tubes of blood of 10 mL before the 3rd treatment (J28 before administration)

- **Every 8 weeks, even if the cures for toxicity are spaced out:**
    - Clinical examination: weight, body surface area, WHO general condition, blood pressure
    - Laboratory workup: Hemoglobin (hemoglobin, PNN, platelets), creatinine, blood ionogram, magnesemia, serum calcium, PT, albuminemia, total, free and conjugated bilirubinemia, transaminases, alkaline phosphatases, LDH, proteinuria (urine test strip) and 24-hour proteinuria if test strip > 2+, INR for patients on VKA.
    - Toxicity evaluation according to NCI-CTCAE version 4.0
    - Morphological evaluation of the disease (every 8 weeks even after cessation of treatment for toxicity, in order to highlight the date of progression):
        - Spiral thoraco-abdomino-pelvic spiral CT scan (TDM-TAP), with and without contrast agent injection
        - In case of contraindication to the injection of iodinated contrast, hepatic or abdominal MRI with gadolinium injection and thoracic scanner without injection.

FOR CENTRALIZED REVIEW:

During the first 12 months, do not forget to keep on CD a copy of each morphological evaluation and the corresponding report (i.e. 6 evaluations + inclusion imaging).

The ARC FFCD will take care of making an anonymized copy of these imaging reports to centralize them at the CRGA on the "FFCD Images" platform using a secure transmission via the company ETIAM.

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7.2 After discontinuation of the treatment for other reason than progression

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

- Clinical examination (weight, general condition WHO, BP)
- Evaluation of toxicities
- Bioassay: CBC, platelets, creatinine, proteinuria (strip) + 24-hour proteinuria if ≥ 2+, INR highly recommended for patients on VKA

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
- Complementary examinations required by their new treatments
- Evaluation of 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 until death.

WARNING: Patients of childbearing age must continue to use effective contraception for at least 6 months after discontinuation of treatment.

7.3 After the treatment discontinuation for progression

Patients will be seen for consultation **30 days after discontinuation of study treatment**:

- Clinical examination (weight, general condition WHO, BP)
- Evaluation of toxicities
- Bioassay: CBC, platelets, creatinine, proteinuria (strip) + 24-hour proteinuria if ≥ 2+, INR highly recommended for patients on VKA

After progression, patients will be seen in **consultation every 3 months for 2 years and then every 6 months until death with** :

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

CAUTION: Patients of childbearing potential should continue to use effective contraception for at least 6 months after discontinuation of therapy.

8. LOGISTIC FOR ANCILLARY STUDY

Study of Treg lymphocytes, monocytes, dendritic cells, PlGF and proangiogenic factors on blood and biopsies

BLOOD

3 heparinized tubes of 10 mL blood

- Before the first treatment course (on the day of the inclusion test or on the day of the first treatment course before administration of the treatment)
- Before the 3rd chemotherapy treatment (D28 before treatment administration)

Sending Kit

Sampling kits will be sent at the opening of each center (2 DHL boxes each containing 3 heparinized 10 mL tubes and the ad hoc forms). Please use the DHL boxes containing the delivery slip to the INSERM unit for study FFCD 1302. After each shipment of DHL boxes, a new DHL box will be sent.

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

:

Dr Magali TERME
Unité INSERM U970, équipe 10
PARCC-HEGP
56, rue Leblanc
75015 PARIS

The delivery time should be 24 hours, with pick-ups in the morning and DHL pick-up in the afternoon to allow delivery the next morning.

NO PICK-UP OR SHIPMENT ON FRIDAYS.

These samples will be analyzed upon receipt and no banking will be done..

BIOPSY/TUMOR SAMPLE

2 to 3 paraffin-embedded diagnostic biopsies or 1 paraffin-embedded tumor block

Sending Kit

After receipt of the form indicating the number of biopsies or tumor blocks to be sent, you will receive a prepaid max letter that will allow the shipment of the samples.

These samples will be sent to:

Dr Magali TERME
Unité INSERM U970, équipe 10
PARCC-HEGP
56, rue Leblanc
75015 PARIS

9. SERIOUS ADVERSE EVENTS (SAE)

Security Assessment Parameters

Safety evaluation will be done by assessing the general and clinical condition of patients and by collecting events occurring between visits during consultations, through regular blood tests. Toxicities will be assessed using the NCI-CTCAE Toxicity Scale version 4.0 (Appendix 6).

In the event of an emergency, the patient, his/her relatives or attending physician should call the investigator to inform him/her of an event.

Definitions

a. Adverse Event (AE)

An adverse event is a harmful occurrence in a person who is involved in biomedical research, whether or not that occurrence is related to the research or the product that is the subject of the research.

All adverse events will be recorded in the case report book on the pages provided.

b. Serious Adverse Event (SAE)

A serious adverse event is considered to be any event that

- Leading to death,
- Involving the vital prognosis,

- Resulting in hospitalization or an extension of 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 mental handicap that is clinically significant and affects the patient's physical activity and/or quality of life.

Any clinical event or laboratory result that is considered serious by the investigator and that does not meet the criteria for seriousness 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: overdoses, second cancers, pregnancies and new developments may be considered medically significant).

c. Undesirable Effect

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

d. Undesirable Effect Serious Unexpected Serious

An unexpected serious adverse reaction is an event not mentioned, or different in nature, intensity, or evolution from the product's reference document (or RCPs).

e. New development

A new fact may be: an unexpected frequency of an expected SAE, a 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 serves as a guide for defining reporting obligations.

The intensity of events will be estimated according to the extract of the CTC-AE classification version 4.0 (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): imposes resuscitation measures / threatens the life prognosis
- 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 study product 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. Sponsor's responsibility

Upon receipt of the serious adverse event report established by the investigator, the sponsor should provide 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 the sponsor to one of the study products (i.e., it is a

serious adverse event), the investigator and/or the sponsor should establish the expected or unexpected nature of the serious adverse event.

If it is an unexpected serious adverse event, or if it is a new development, the sponsor prepares an initial report that will be sent to the ANSM, the CPP and the EMA (via EudraVigilance) within 7 days in the case of death or life-threatening events, otherwise within 15 days.

If it is an expected serious adverse reaction, it will be collated for the drafting of semi-annual and annual safety reports.

Events not to be considered as serious

The progression of the disease should not be considered as a SAE.

Events potentially related to the progression but which may also be secondary to the treatment will continue to be reported (e.g. thromboembolic events, haemorrhagic phenomena, perforations, etc.).

Because of the seriousness of the disease in this study, certain conditions defined as SAEs will be excluded from the procedure for declaring a SAE, namely :

- Hospitalization or surgery specifically related to the treatment of the disease
- Hospitalization performed to simplify treatments or study procedures

In this essay the reference documents will be :

- For aflibercept, the Investigator's Brochure (provided in the Investigator's Binder)
- For 5-fluorouracil, the Summary of Product Characteristics of Fluorouracil Ebewe® 50 mg (Appendix 7)
- For Folinic Acid, the ELVORINE® Summary of Product Characteristics (Appendix 7)
- For irinotecan, the Summary of Product Characteristics of Campto® (Appendix 7)

The versions of the PCRs used to define the expected or unexpected character will be the latest available on the anniversary date of the trial start.

Course of action

The investigator informs the sponsor of all Serious Adverse Events (Expected and Unexpected), whether or not they are attributable to the research, that occur during the study or within 30 days after the last administration of treatment.

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

The report shall be made by faxing the "notification of a serious adverse event" form (Appendix 8), documented as precisely as possible, dated and signed, within 24 working hours following their observation to the Centre de Randomisation Gestion Analyse (CRGA) of the FFCD: by fax to 03 80 38 18 41.

The investigator is responsible for the appropriate medical follow-up of patients until the resolution or stabilization of the effect or until the death of the patient. This may sometimes imply that this follow-up continues after the patient is discharged from the trial.

Additional information is sent to the sponsor using an SAE reporting form (by checking the "Follow-up" box and incrementing the number to indicate that it is a follow-up report and not an initial report) within 24 hours of receiving it. It also transmits 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

10.1 Judgement endpoint

10.1.1 Main efficacy criteria

The primary endpoint is the investigator's rate of alive and progression-free patients at 6 months.
Progression is defined by :

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

10.1.2 Secondary criteria

Secondary criteria are :

- Overall survival is defined as the time from the date of inclusion of the patient to the patient's death, or the date of last news if the patient is alive.
- Alive and progression-free rate at 6 months (RECIST version 1.1) based on centralized review.
- Progression-free survival is defined as the time from the inclusion date to the date of first radiological progression as assessed by the investigator using the RECIST version 1.1 criteria or death (from any cause) or the latest news date if the patient is alive and progression-free.

Overall survival and progression-free survival will be estimated at 2, 4, 6 and 12 months after inclusion and medians will also be estimated.

- Time to progression is defined as the time from the inclusion date to the date of progression as assessed by the investigator using the RECIST criteria version 1.1.
- Objective response rate (OR and OR) is defined as the number of patients with OR or OR, as assessed by the investigator using RECIST criteria version 1.1 at 2, 4, 6 and 12 months.
- Time to objective response (CR and PR) is defined as the time from the date of inclusion to the date of complete or partial response, as assessed by the investigator using RECIST criteria version 1.1.
- The rate of disease control (CR, PR and SD) is defined as the number of patients with CR, PR or stable disease, as assessed by the investigator using RECIST criteria version 1.1 at 2, 4, 6 and 12 months.
- Duration of disease control is defined as the time from the inclusion date to the date of first progression in patients with a complete response, partial response or stable disease, as assessed by the investigator using RECIST criteria version 1.1.
- The rate of live, progression-free patients at 6 months, as assessed by central review.
- Rate of best response (CR, RP, SD or P), as assessed by the investigator using RECIST version 1.1 criteria.
- Toxicities will be described according to the NCI-CTCAE classification version 4.0 and according to grades.

10.2 Sample size calculation

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

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

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

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

Step 1 : Over 33 first patients
- If 20 or less than 20 patients are alive without any progression at 6 months, the study will be stopped ;
- If 21 or more than 21 patients vivants are alive without any progression at 6 months, study will continue

Inclusion will be stopped between step 1 and 2.

At the end of step 2, over 49 patients
- If 32 or less than 32 patients are alive without any progression at 6 months, the treatemnt will be considered as inefficient
- If 33 or more than 33 patients are alive without any progression at 6 months, the treatemnt will be considered as efficient

The analysis of the primary endpoint will be performed in terms of intention to treat for all evaluable patients included in the study regardless of eligibility criteria and treatment received.

The decision rules may be adapted according to the actual number of patients included in the trial.

Patients not evaluated at 6 months will be reviewed according to the following rules:
- If the patient has a later evaluation (7 months or more) and is not progressing at that time then he will be considered progression-free at 6 months.
- If the patient has a documented progression within 2 months after 6 months then this patient will be considered to be progressing at 6 months. If the progression is documented beyond 8 months then the patient will not be considered progressive at 6 months.

If a progression is documented prior to the 6-month assessment, the patient is considered to be progressing at 6 months.
A patient who has not had an assessment for more than 12 months is considered lost to follow-up.

10.3 Statistical analysis plan

Populations

The patients included in the study will be described.

Analyses will be performed with intent to treat (ITT): all patients included in the study regardless of eligibility criteria and treatment received.

A per-protocol analysis (PP) of the primary endpoint will also be performed. The IP population is defined as ITT patients without major protocol violations, having received at least one dose of treatment and having at least one tumor evaluation within 6 months of treatment.

Safety evaluable population: the ITT population having received at least one dose of treatment.Analyses principales

A statistical analysis plan will be written before the database is frozen.

Clinical variables will be described using percentages (95% confidence interval), mean (standard deviation) and median (Q1, Q3, Interquartile Interval, minimum and maximum).

Survival and time estimation will be done using the Kaplan Meier (KM) method. They will be described by medians and rates at different temporalities with their 95% confidence intervals.

The median follow-up time will be calculated using the reverse KM method.

10.4 Independant commitee

An independent committee will be formed and will include at least two physicians, a statistician and a pharmacovigilance expert. The independent committee will meet every 6 months during the treatment period to decide on the tolerance data. It may be consulted at any time during the protocol when the sponsor deems it necessary.

10.5 Imaging Review Committee/Radiology Panel

Anonymized copies of the evaluation reports will be centralized at the CRGA on the "FFCD Images" platform using a secure transmission via ETIAM.
They will be reviewed at a later date by a panel of independent radiologists, who will confirm answers and progress dates once all of the study's exams have been retrieved.

10.6 Steering committee

A Steering Committee will be set up. It will be chaired by the coordinator of the study, Pr. Julien TAIEB. This committee will also include the president of the SDFC, the SDFC statistician and the president of the Biological Research Committee (if applicable). Its mission will be, among others, to take decisions related to the management of the research (amendment, premature closure if necessary, ...).

10.7 Biological committee

A Biological Research Committee will be established and its mission will be to manage problems related to sampling and banking as well as the organization of their analysis. The committee will meet regularly and will report on its proposals to the Board of Directors. This committee will include among others the study coordinator and a biologist; the president of this committee will be Dr. Magali TERME.

11. BACKGROUND INFORMATION AND RATIONALE FOR THE STUDY

Colorectal cancer is the 3rd most common cancer. In 2008, 1.24 million new cases were diagnosed worldwide and mortality due to this cancer was over 600,000 1(Ferlay 2010). The prognosis depends mainly on the extension of the disease to diagnosis. The 5-year survival rates are approximately 90% for localized stages at diagnosis, 60-65% in case of lymph node or neighbor organ invasion and only 5-8% in case of distant metastasis[2] (Chu 2011). Despite the

fact that 75-80% of tumors are resectable at the time of diagnosis, nearly half of the patients will develop metastatic disease. Although mortality rates have been reduced due to new treatment options, once the metastatic stage is reached, median overall survival is a maximum of 24 months. The median survival was 21.5 months in patients treated with FOLFIIRI in the first line and then FOLFOX6 in the second line (n=109) and 20.6 months in patients treated with FOLFOX6 and then FOLFIRI (n=111), [3](Tournigand, 2004).

At the metastatic stage, one of the current therapeutic options is dual cytotoxic chemotherapy (FOLFIRI or FOLFOX) combined with targeted therapy (bevacizumab or anti-EGFR in the case of wild type KRAS status). Bevacizumab is a humanized monoclonal antibody that targets VEGF-A. It has shown a benefit in terms of progression-free survival (PFS), and less consistently in overall survival (OS), in first-line combination with FOLFOX or FOLFIRI [4-6] (Saltz 2008, Hurwitz 2004) and in second-line combination with FOLFOX 7 (Giantonio, 2005). Cetuximab is a chimeric anti-EGFR. The Phase III CRYSTAL study comparing FOLFIRI with and without cetuximab in the first line showed an improvement in response rate and PFS in patients who received cetuximab[8] (Van Cutsem 2007). However, in this study there was no statistically significant difference between the 2 arms in overall survival. Patients with KRAS mutations do not benefit from treatment with cetuximab in combination with either FOLFOX or FOLFIRI[9, 10] (Van Cutsem 2008, Bokemeyer 2009). In a study comparing these targeted therapies combined with FOLFIRI as a first-line treatment for mRCC, objective response rates (evaluated according to RECIST criteria) of 44% to 48% and progression-free survival of 7.5 to 8.9 months[11] (Stintzing 2012) were found. This study therefore shows the efficacy of these triple therapies but does not allow to determine the superiority of one of the 2 treatments over the other. The tolerance of these treatments was acceptable compared to dual chemotherapy alone.

These trials show the value of adding a targeted therapy to cytotoxic chemotherapy as a first-line treatment for patients with metastatic colorectal cancer.

Recently, aflibercept, a novel anti-angiogenic molecule targeting VEGF-A, VEGF-B, and PlGF (Placental Growth Factor), showed efficacy as a second-line treatment in patients with metastatic colorectal cancer in the VELOUR[12] phase III trial (Van Cutsem, 2012). The 1,226 patients who progressed after a first line of chemotherapy including oxaliplatin were included and randomized to either a FOLFIRI arm alone or a FOLFIRI arm + aflibercept. Survival (overall and progression-free) was statistically significantly increased in the FOLFIRI + aflibercept arm compared to the FOLFIRI + placebo arm (OS: 13.5 vs. 12.1 months, PFS: 6.9 vs. 4.7 months). In this trial, patients had received FOLFOX +/- bevacizumab as a first-line treatment for their mRCC and interestingly, even patients initially treated with bevacizumab (28%) benefited from the addition of aflibercept to chemotherapy. This suggests that this molecule could overcome resistance mechanisms to other anti-angiogenic treatments.

There are currently no data on the combination of FOLFIRI + aflibercept as a first-line treatment for patients with mRCC.

In addition, the immune system has been shown to play an important role in the control of tumor development and growth. Tumors develop mechanisms of escape from the immune system, such as the induction of immunoregulatory cells such as regulatory T lymphocytes (Treg). These regulatory cells are capable of reducing the host's anti-tumor immune response, thereby promoting tumor growth and metastatic spread. Modulating these regulatory cells could therefore make it possible to restore an effective immune response against the tumor and allow better control of its development. Certain pro-angiogenic factors are probably involved in the modulation of the immune system by tumors. Indeed, their receptors are present on certain immune cells. We have shown that VEGF can have a direct effect of induction of Treg proliferation via an action on VEGF-receptor 2 expressed by Treg [13] (Term et al Cancer Res 2013). VEGF could also have an indirect action mediated by the induction of immature dendritic cells. Several trials have shown that anti-angiogenic therapies have a positive action on the modulation of Treg in different mouse tumor models. In humans, the proportion of Treg is increased in the peripheral blood of patients with metastatic CRC compared to healthy volunteers. We have shown a decrease in the proportion of Treg in the peripheral blood of patients with metastatic CRC treated with bevacizumab in a first-line setting compared to patients treated with chemotherapy alone[13] (Term 2013). Both VEGF and PlGF are capable of inhibiting dendritic cell (DC) maturation[14]

(Dikov 2005). To our knowledge, there are no data in the literature regarding the immunomodulatory effects of aflibercept on Treg and DC in humans.

Therefore, aflibercept targets not only VEGF-A and B but also the Placental Growth Factor (PlGF). The Placental Growth Factor (PlGF) is a member of the VEGF family and is attached to the VEGFR-1 receiver. It acts in particular on the growth and maturation of blood vessels by promoting the proliferation, migration and survival of endothelial cells. Tumor cells but also stromal cells can produce PlGF. PlGF levels are correlated with tumor stage, metastatic invasion and inversely with survival in different solid tumors[15] (Dewerchin 2012). PlGF can therefore promote tumor growth by stimulating blood vessel growth, but it also has immunomodulatory properties (recruitment of inflammatory cells, polarization of tumor infiltrating macrophages towards a pro-angiogenic macrophage phenotype, inhibition of dendritic cell maturation)[14] (Dikov 2005).

Targeted therapies for VEGF increase serum PIGF levels in patients with mRCC[16] (Kopetz JCO 2010). PlGF may attract VEGFR1-expressing cells to the tumor and thus contribute to resistance to anti-angiogenic therapies. Administration of aflibercept in patients with relapsed glioblastoma results in a decrease in a portion of VEGFR1-expressing monocytes (CD14+ VEGFR1+), associated with radiological response to treatment[17] (de Groot 2011). Therefore, we propose to analyze different monocyte subpopulations in patients with metastatic CRC treated with aflibercept.

Finally, while VEGF-A has been studied in patients with CRC, there is very limited data on VEGF-B and PlGF (aflibercept target molecules). We therefore propose to analyze these different pro-angiogenic factors in patient plasma before and after 2 treatment cycles. On the other hand, PlGF expression could be analyzed by immunohistochemistry in tumors collected before treatment.

This Phase II trial will evaluate the efficacy and safety of the combination aflibercept + FOLFIRI as first-line treatment in mRCC patients with an ancillary project that aims to test cytokines and monocytes, DC and Treg before and after treatment. The prognostic value of the response to aflibercept of these immune parameters will be analyzed.

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13. ADMINISTRATIVE CONSIDERATIONS

STUDY PROMOTOR

The promoter of the study is the Fédération Francophone de Cancérologie Digestive (FFCD). The study has been registered under the number EudraCT 2013-004081-33.

REMINDER OF THE TEXTS IN FORCE

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

CIVIL LIABILITY INSURANCE

An insurance was subscribed by the promoter on 02/10/2013 under number 137.681, in accordance with article L 1121-10 of the Public Health Code (Annex 11).

REQUEST FOR AUTHORIZATION FROM THE CPP AND THE ANSM

This protocol was authorized by the CPP (Committee for the Protection of Persons) ILE DE France VIII of Boulogne Billancourt on 19/12/2013 (Annex 11).
This protocol received a favorable opinion from the ANSM (Agence Nationale de Sécurité du Médicament et des Produits de Santé) on January 30, 2014 (Annex 12).

PATIENT'S CONSENT

The investigator undertakes to collect the patient's written clinical and biological consents (information sheets and consent forms in Appendices 1 and 2) prior to the patient's inclusion 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.

INFORMATION TO HOSPITAL MANAGEMENT AND RESEARCH AGREEMENT

Prior to the implementation of the study, hospital management will be informed by the sponsor of the investigator's interest in participating in this trial.
A research agreement will be established at no extra cost between the administrator of the investigator center and the sponsor.

DATA ARCHIVING

The records will remain confidential and can only be consulted under the responsibility of the physicians 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 case report 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 liberties, the trial data will be recorded in a computer database of the FFCD's Randomization and Management Analysis Center, excluding elements relating to the identity of patients.

DATA PROCESSING

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

MONITORING, QUALITY ASSURANCE AND INSPECTIONS BY THE AUTHORITIES

The investigator agrees in advance that the included patient records may be consulted by a person mandated by the FFCD and/or by the health authorities to conduct an audit. On-site file visits, scheduled after agreement of the investigator, may take place during or after the inclusion period in the trial.
This protocol will be monitored by the SFFCD's mobile CRAs.