PARTENARIAT DE RECHERCHE EN ONCOLOGIE DIGESTIVE

PRODIGE 45 - FFCD 1408 - HIGH-LIGHT
RANDOMIZED PHASE II EVALUATION OF EFFICACY AND TOLERANCE OF 2 THERAPEUTIC STRATEGIES COMBINING BEVACIZUMAB WITH CHEMOTHERAPY: DE-ESCALATION VERSUS ESCALATION IN PATIENTS WITH UNRESECTABLE, NON-PRE-TREATED METASTATIC COLORECTAL CANCER

EudraCT n°: 2016-001225-13

COORDINATOR (FFCD representative)
Prof. Jean-Marc PHELIP
Saint Etienne University Hospital - Hôpital Nord
HGE Department
108 rue Albert Raimond - BP 60008
42277 SAINT PRIEST EN JAREZ
Tel: 04 77 82 83 20; Fax: 04 77 82 84 52
E-mail: j.marc.phelip@chu-st-etienne.fr

SCIENTIFIC CO-RESPONSIBLES (representing UNICANCER GI)
Dr Valérie BOIGE Digestive Oncology Department
Department of Oncology Medicine
Gustave Roussy
Tel: 01 42 11 43 11
E-mail: valerie.boige@gustaveroussy.fr

PROTOCOL **DRAFTING COMMITTEE**
JM Phélip, J Bennouna, K Le Malicot, M Schneider

TRANSLATIONAL RESEARCH COMMITTEE
D Tougeron, T Lecomte, P Laurent-Puig

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

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

Statistician: **Karine LE MALICOT**
Tel: + 33 (0)3 80 39 34 71 - Fax: + 33 (0)3 80 38 18 41
E-mail: karine.le-malicot@u-bourgogne.fr

Project manager: **Lila GABA-BERKOUK**
Tel: + 33 (0)3 80 39 34 04 - Fax: + 33 (0)3 80 38 18 41
E-mail: lila.gaba@u-bourgogne.fr

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

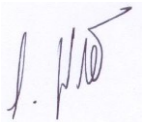
ACE	Carcinoembryonic antigen
AF	Folinic acid (leucovorin)
ALAT	Alanine aminotransferase (or SGPT: serum glutamic pyruvic transaminase)
ASAT	Aspartate aminotransferase (or SGOT: serum glutamic oxaloacetic transaminase)
BPC	Good Clinical Practice
JRC	Colorectal carcinoma
CCRm	Metastatic colorectal carcinoma
CIRD	Independent data review committee
CO	Observation notebook
CT	chemotherapy
DPD	dihydropyrimidine
ECG	Electrocardiogram
EI	Undesirable event
EIG	Serious adverse event
5-FU	5-fluorouracil
FFCD	French-speaking Federation of Digestive Oncology
FOLFIRI	5-fluorouracil, leucovorin and rinotecan
FOLFOX-4	5-fluorouracil, leucovorin and oxaliplatin
MODIFIED FOLFOXIRI	5-fluorouracil, leucovorin, irinotecan and oxaliplatin
HR	Hazard ratio
IC	Confidence interval
BMI	Body mass index
MRI	Magnetic resonance imaging
iv	Intravenous
j	Day
NCI-CTCAE	National Cancer Institute - Common toxicity criteria for adverse events
p.o.	Per os
PAL	Alkaline phosphatases
PAD	Diastolic blood pressure
NOT	Systolic blood pressure
QDV	Quality of life
RECIST	Criteria for evaluating tumor response in solid tumors
SG	Overall survival
SSP	Progression-free survival
TAP	Thoracoabdomino-pelvic
CT SCAN	Computed tomography
vs.	Versus

PROTOCOL AGREEMENT AND BPC

PRODIGE 45 - FFCD 1408 - HIGH-LIGHT
RANDOMIZED PHASE II EVALUATION OF EFFICACY AND TOLERANCE OF 2 THERAPEUTIC STRATEGIES COMBINING BEVACIZUMAB WITH CHEMOTHERAPY: DE-ESCALATION VERSUS ESCALATION IN PATIENTS WITH UNRESECTABLE, NON-PRE-TREATED METASTATIC COLORECTAL CANCER

EudraCT n°: 2016-001225-13

This version of the protocol is approved by :

Developer: Ms Cécile GIRAULT Date: 06/17/2016Signature  :

The Coordinator: Pr Jean-Marc PHELIPDate : 17/06/2016Signature: 

I, the undersigned, Doctor

Having read the requirements for this research, the protocol and its appendices, I hereby certify that I will conduct this trial in compliance with the regulations in force.
In particular, I undertake to :
- respect the protocol and any modifications notified to me by the Promoter
- agree to supervise research in the center and to train my collaborators in the conduct of research and to provide a list of their names
- have each patient sign a written consent form, after having read the patient information leaflet, before any research is carried out
- report serious adverse events or new facts to the promoter within 24 hours of becoming aware of them
- respect inclusion and non-inclusion criteria, as well as study start and end dates
- participate in the biological part of the study, subject to the patient's signing a specific consent form and sending samples as recommended
- complete all items in the observation book, ensure quality data collection and proper product management
- keep research data and documents for 15 years after the end of the study
- inform the Promoter of any conflict of interest that may affect my scientific independence in the context of the research.
- inform the Promoter without delay of any action, whether amicable or contentious, brought by a person taking part in the research or his successors or assigns, likely to call into question the Promoter's liability
- accept periodic visits from the ARC FFCD and make available to them all source documents and materials relating to the research, so that they can check the data recorded in the observation book.
- accept an audit by the Promoter and/or an inspection by the health authorities
- respond to requests for corrections or clarifications to the observation booklet
- give the ARC FFCD the time it needs to sign the forms, answer any questions and take action.

Date : Signature :

CENTER STAMP :

Send original to CRGA de la FFCD - 7 bd Jeanne d'Arc - BP 87900 - 21079 Dijon Cedex - France

CONTACTS FFCD

NAME	FUNCTION	TELEPHONE	TELECOPIE	EMAIL
RANDOMIZATION CENTER - MANAGEMENT - ANALYSIS				
Lila GABA-BERKOUK	Project Manager	03 80 39 34 83	03 80 38 18 41	lila.gaba@u-bourgogne.fr
Coralie DEVORSINE	Assistant Project Manager	03 80 39 34 86	03 80 38 18 41	coralie.devorsine@u-bourgogne.fr
Karine LE MALICOT	Statistics Manager	03 80 39 34 71	03 80 38 18 41	karine.le-malicot@u-bourgogne.fr
Paolo CARNI	Data Manager	03 80 39 34 53	03 80 38 18 41	paolo.carni@u-bourgogne.fr
Mickaël VOYE	Assistant Data Manager	03 80 39 34 53	03 80 38 18 41	mickael.voye@u-bourgogne.fr
Caroline CHOINE-POURRET	ARC Coordinator	04 69 18 19 02	09 74 44 22 47	carolinechoine.ffcd@sfr.fr
For contact details of the FFCD ARC responsible for your center : - please contact Caroline CHOINE or - visit the FFCD website: http://www.ffcd.fr/index.php/organisation-pro/cartographie/arcnew				

You can also contact the FFCD's CRGA on: 03 80 66 80 13
(Monday to Friday from 9H00 to 18H00)

SUMMARY

Title	**PRODIGE 45 - FFCD 1408 - HIGH-LIGHT** **RANDOMIZED PHASE II EVALUATION OF EFFICACY AND TOLERANCE OF 2 THERAPEUTIC STRATEGIES COMBINING BEVACIZUMAB WITH CHEMOTHERAPY: DE-ESCALATION VERSUS ESCALATION IN PATIENTS WITH UNRESECTABLE, NON-PRE-TREATED METASTATIC COLORECTAL CANCER**
Developer	FFCD
Type	Phase II randomized non-comparative multicenter study
Objectives	**Main objective** The primary objective is to evaluate the rate of patients without strategy failure 16 months after randomization. Strategy failure is defined by: • Progression (defined in each arm)* using RECIST v1.1 criteria or • Deaths (all causes) or • Toxicity leading to permanent discontinuation of one of the chemotherapy products (oxaliplatin and irinotecan) or • Patient's refusal to continue the strategy or • Investigator's decision to discontinue strategy ***Progression is defined differently** depending on the treatment arm because the two strategies are different: - **In the standard** (climbing) **arm**, progression is considered a failure: • If it occurs during 1ère chemotherapy with LV5FU2 + bevacizumab and 2ème chemotherapy with FOLFIRI + bevacizumab cannot be administered • if it occurs during 2ème chemotherapy with FOLFIRI + bevacizumab and if 3ème chemotherapy with FOLFOX + bevacizumab) cannot be administered e or • if it occurs during 3 ème chemotherapy - **In the experimental strategy** (de-escalation), progression is considered a failure: • if it occurs during chemotherapy with modified FOLFOXIRI + bevacizumab or FOLFIRI + bevacizumab. Progression during treatment with capecitabine + bevacizumab does not constitute failure of the strategy. **Secondary objectives** The secondary objectives are: • Best response according to RECIST version 1.1 at 16 months • Time to best response during the strategy • Time to strategy failure • Progression-free survival (PFS) at 2 and 3 years over the course of the strategy • Overall survival (OS) at 2 years and 3 years • Tolerance of both strategies • The dose intensity for each treatment and the duration of the strategy • Quality of life (EORTC QLQ-C30) • The relationship between progression-free survival and BMI
Population	**Inclusion criteria:** - Histologically proven metastatic colorectal cancer (on primary tumor and/or metastases) - Non-resectable and non-pretreated metastases - Unmutated BRAF - Patient considered suitable for treatment strategies - At least one measurable target lesion > 1 cm according to RECIST 1.1 - Tumor evaluation according to RECIST, performed no more than 21 days before randomization - Age ≥ 18 years - WHO performance index ≤ 2 - Life expectancy over 3 months - Biological profile: PNN≥1,500/mm^3 , platelets≥100,000/mm^3 , hemoglobin>9 g / dL - Creatinine clearance (Cockcroft and Gault formula)>30mL/min, serum creatinine<1.5LSN - Liver workup: total bilirubinemia <1.5xLSN, ASAT/ALAT≤5LSN , alkaline phosphatases ≤ 2.5 x LSN (or ≤ 5 x LSN in case of liver invasion), if urine dipstick proteinuria ≥ 2+ then 24 h proteinuria < 1 g - Women of childbearing age and men (who have sexual relations with women of childbearing age) must undertake to use effective contraception without interruption for the duration of treatment and for 6 months following the last administration - Signed clinical informed consent - Patient affiliated to a social security scheme

	Non-inclusion criteria: - Any patient with potentially resectable colorectal cancer, i.e. for whom the aim of chemotherapy is to render all metastases resectable. - Peripheral sensory neuropathies Grade >1 - Patients with symptomatic metastases - Symptomatic tumor in place (occlusion, hemorrhage) - Active peptic ulcer, wound or bone fracture - Inflammatory bowel disease, extensive small bowel resection - Clinically significant active heart disease or myocardial infarction within the last 6 months. - Hypertension not adequately controlled - QT/QTc interval > 450 msec for men and QT/QTc interval > 470 msec for women on ECG at inclusion - K^+ < LIN, Mg^{2+} < LIN, Ca^{2+} < LIN - Known DPD (Dihydropyrimidine dehydrogenase) deficiency - Major abdominal or extra-abdominal surgery (except diagnostic biopsy) or irradiation within 4 weeks prior to the start of randomization. - Adjuvant chemotherapy within 4 months of randomization - Previous treatment with an anti-angiogenic agent or irinotecan - Metastases or suspected metastases in the central nervous system - History of malignant pathologies in the last five years, with the exception of properly treated basal cell skin carcinoma or carcinoma in situ of the uterine cervix - Macronodular peritoneal carcinosis - History of hemoptysis ≥ grade 2 (defined as ≥ 2.5 mL of bright red blood per episode) in the month prior to inclusion - Known hypersensitivity to any component of bevacizumab or to any of the study treatments - Active infection requiring intravenous antibiotics at the start of treatment - History of abdominal fistula, gastrointestinal perforation, intra-abdominal abscess or active gastrointestinal bleeding in the 6 months preceding the start of the strategy. - Pregnant or breast-feeding women - Concurrent participation in another clinical drug study during the treatment phase and 30 days before starting the study strategy - Patient unable to undergo medical follow-up for geographical, social, psychological or legal reasons.
Diagram and stratification	Phase II, open-label, multicenter, randomized, non-comparative study evaluating the efficacy and safety of two treatment strategies combining bevacizumab with chemotherapy in patients with untreated, unresectable, non-mutated BRAF mRCC. Patients will be randomized in: **Standard strategy (A-arm climbing strategy):** Patients will start the strategy with 1ère chemotherapy based on LV5FU2 (or capecitabine) + bevacizumab. After progression, they will receive 2ème chemotherapy with FOLFIRI + bevacizumab. After progression, they will receive 3ème chemotherapy with FOLFOX4 + bevacizumab. When progression occurs during 3ème chemotherapy or if 3ème chemotherapy cannot be administered, patients will be treated according to the investigator's choice. The duration of a chemotherapy cycle is 14 days, or 21 days if the patient is receiving capecitabine. **Experimental strategy (de-escalation strategy - arm B):** Patients will receive 4 cycles of modified FOLFOXIRI + bevacizumab followed by 4 cycles of FOLFIRI + bevacizumab and then maintenance treatment with capecitabine and bevacizumab until progression. After progression during maintenance treatment, the patient will resume treatment with 4 cycles of modified FOLFOXIRI + bevacizumab, then 4 cycles of FOLFIRI + bevacizumab, followed by maintenance treatment with capecitabine and bevacizumab until progression etc. The duration of a chemotherapy cycle is 21 days for maintenance cycles with capecitabine. If progression occurs during treatment with modified FOLFOXIRI + bevacizumab or FOLFIRI + bevacizumab, patients have failed the strategy and will be treated according to the investigator's choice. Tumor response and disease progression will be assessed in both arms at the same rate: at most 21 days before randomization, then every 8 weeks according to RECIST version 1.1 criteria.

	Randomization will be carried out on a 1:1 basis using the minimization technique with the following stratification factors: - Center - WHO performance index 0/1 vs 2
Treatment and follow-up	**Processing :** Patients will be treated until : Unacceptable toxicity Strategy failure as defined in primary endpoint Patient refusal or investigator's decision **Follow-up:** Patients will be followed until : Strategy failure or at the latest up to 3 years after last patient included Withdrawal of consent
Number of patients and statistical analysis	The study's primary endpoint is the failure rate of the strategy 16 months after randomization. The clinical hypotheses for the study design are as follows: H_0 : A rate of 40% of patients alive and without strategy failure at 16 months is not interesting. H_1 : A live patient rate without strategy failure at 16 months of 55% is expected. With an α (one-sided) risk of 5% for a power of 80.85%, using an exact binomial method, 75 patients will be randomized to each strategy. Taking into account that 10% of patients in the ITTm population cannot be evaluated, **84 patients per strategy will be randomized in a** 1:1 ratio (**168 patients in total**). (**ITTm population**: patient having received at least one dose of chemotherapy and having an imaging evaluation during the strategy). The conclusion of the study will be based solely on the experimental arm according to the rule defined below on the first 75 evaluable patients: • If 38 or more patients are alive and have not failed the strategy at 16 months, then the strategy is considered effective. The characteristics of the population at inclusion (on the ITT population) will be described using descriptive statistics in the form of percentages for qualitative variables, and the mean (standard deviation), median (with inter-quartile range, minimum and maximum) for continuous variables. Results are presented by treatment strategy and for the overall population. For the primary endpoint (mITT and ITT populations), a one-sided 95% confidence interval will be calculated. For efficacy criteria (mITT and ITT populations), survival data (OS and PFS) will be estimated from the date of randomization, using the Kaplan-Meier method. Results will be presented by strategy. All toxicities (Population Tolerance) will be described by strategy.

	A statistical analysis plan (SAP) will be drawn up before the database is frozen.
Ancillary studies	**Organic :** • Demonstrate the impact of RAS mutations on response to bevacizumab in mRCC • Demonstrating the impact of thymidilate synthase (TS) polymorphism • Prospectively determine the frequency of tumor patients with low levels of mutated RAS alleles. • Evaluate the use of a new, highly sensitive technique for determining RAS status in blood. • Analyze the correlation between the level of mutated RAS alleles in the primary tumor and peripheral blood. • Analyze changes in the rate of mutated RAS alleles over time. • Assess circulating VEGF (at time of diagnosis and every 2 cures) **Imaging :** • Assessing the relationship between PFS and tumor size at diagnosis • Evaluate the relationship between PFS and visceral fat (measured by CT scan at inclusion)
Estimated study duration	The study will last approximately 6 years from the inclusion of the first patient (3 years of recruitment, 2 years of treatment and 3 years of follow-up). Inclusion rates are estimated at between 10 and 11 patients per month. First theoretical inclusion: 2ème quarter 201 6

STUDY SCHEDULE

	Pre-inclusion (≤ 7 days)	Before each cycle	Every 8 weeks	End of treatment	After discontinuation of protocol treatment [6]
Signed consent	x				
Medical history	x				
Clinical examination with vital signs (blood pressure, pulse), WHO, weight, height	x	x	x	x	x
RAS status [1]	x				
ECG	x	x[7]	x[7]	x	
Abdominal and pelvic CT or thoracic CT + abdominal and pelvic MRI[2]	x		x		x
Bone scan/skeletal X-ray for suspected bone metastases	x				
Cerebral CT in cases of suspected brain metastases	x				
Pregnancy test[3]	x				
Biological check-up	x[4]	x[5]	x[4]	x[4]	x[4]
Tumor markers: ACE, LDH	x		x		x
Toxicity assessment		x		x	
Quality of life (QLQ-C30)	x		x		x
Translational research: tumor and blood samples (before C1, C2, C5 and C8)	x				

[1]If KRAS status is not available at inclusion, it will be reported in the case report when available.
[2]Baseline imaging to be performed within 21 days of inclusion: thoraco-abdomino-pelvic CT scan (TAP), without and with contrast injection. **Send a copy of the baseline CT scan to the CRGA for centralized review, as well as the 2-month CT scan in arm B.**
If injection of iodinated contrast is contraindicated, a liver or abdominal MRI with injection and a thoracic CT scan without injection can be performed.
[3]For women of childbearing age
[4]Complete biological workup: CBC/platelets, blood ionogram (Na, K, Ca), creatinine, protid, albumin, liver workup including ASAT, ALAT, PAL, GGT, total and conjugated bilirubin, PT, TCK, urine dipstick with 24-hour proteinuria if ≥ 2+, creatinine clearance. If dipstick ≥ 2+: 24-hour proteinuria result must be ≤ 1 g protein to be eligible
[5] Pre-cure workup: CBC/platelets, creatinine, AST, ALT, bilirubinemia, proteinuria by dipstick supplemented by 24-hour proteinuria if > 2 +.
[6] Monitoring: - if the protocol strategy is discontinued due to progression, clinical monitoring is maintained every 3 months for 2 years, then every 6 months for 1 year. - if treatment is stopped before tumor progression (toxicities or patient refusal), clinical and biological monitoring, tumor evaluation by imaging and quality of life are continued every 8 weeks. After progression, patients will be seen in consultation every 3 months for 2 years, then every 6 months for 1 year.
[7] : ECG before and at the end of each intravenous oxaliplatin infusion

1 INTRODUCTION - RATIONALE FOR THE STUDY

1.1 Treatment of metastatic colorectal cancer

The multiplicity of therapeutic weapons and their very different modes of action mean that we can now envisage innovative strategies for the management of metastatic colorectal cancer.

Optimization of tumor response (by bi- or tri-chemotherapy + biotherapy) has shown its value not only in terms of secondary resectability of metastases, but also in improving prognosis in patients with unresectable metastases.

The intensity of tumor response also seems to correlate with the feasibility and duration of a therapeutic pause or light maintenance treatment (1,2) maintained until progression in patients initially controlled by "induction" chemotherapy. Bevacizumab combined with cytotoxic chemotherapy (5FU, irinotecan and/or oxaliplatin) has been shown to improve tumor response rates (60% partial responses) and prognosis in patients with 1ère and 2ème metastatic lines (overall survival of around 25 months). Its highly favorable safety profile makes it an excellent candidate for both induction (3, 4, 5, 6) and maintenance treatment. Prospective data from recent phase II and III trials have demonstrated an improvement in PFS and/or overall survival by maintaining bevacizumab alone or in combination with 5FU (or capecitabine) after disease control with 2 to 3 months of induction chemotherapy (FOLFIRI or FOLFOX + bevacizumab) (1, 7, 8). These treatments are listed in the TNCD (http://www.tncd.org/).

At the same time, the maintenance of antiangiogenic pressure after progression in 1ère metastatic line (with switch of cytotoxic chemotherapy) has demonstrated its benefit in terms of PFS and overall survival (9, 10, 11). Maintaining bevacizumab in 2ème metastatic lines, despite progression, therefore appears to be a valid strategy. The molecule's action on "healthy" vascular endothelium means that "primary" resistance phenomena cannot be envisaged. This concept of continuous blockade of angiogenesis is therefore conceivable for subsequent lines of treatment, but there is no current data to validate it.

1.2 Rational for the de-escalation strategy

Three phase III trials have compared a "top-down" strategy of induction with bi-chemotherapy (5FU + irinotecan or oxaliplatin), followed at progression by a switch to irinotecan and oxaliplatin, with a "bottom-up" strategy in which 5FU is started alone, followed at progression by the introduction of oxaliplatin or irinotecan. The results of these trials are consistent, showing no difference in prognosis and overtoxicity in patients starting with bi-chemotherapy (12, 13, 14). However, biotherapy was not included in these trials, and response rates were low, with overall survival of around 16 months. There is therefore currently a conflicting debate about the value of an ascending vs. descending strategy in patients with unresectable metastases. To date, no trial has evaluated these two strategies in combination with biotherapies, i.e. with optimized chemotherapy capable of producing high response rates and prolonged survival, and allowing maintenance treatment.

Thus, the aim of this work is to combine continuous blockade of angiogenesis by bevacizumab delivered to the first 3 metastatic lines in a strategic randomized phase II trial evaluating a "top-down" strategy of upfront optimization with 4 courses of modified FOLFOXIRI-bevacizumab and 4 courses of FOLFIRI-bevacizumab followed by maintenance treatment with 5FU-bevacizumab until progression (retreatment with 5FU-bevacizumab).bevacizumab and 4 courses of FOLFIRI-bevacizumab followed by maintenance treatment with 5FU-bevacizumab until progression (reintroduction of induction in the event of progression) versus a "bottom-up" strategy with 5FU-bevacizumab followed from the outset, upon progression, introduction of irinotecan followed by oxaliplatin, with continued angiogenesis blockade by bevacizumab. The chosen endpoint was the failure rate of the strategy at 16 months for phase II.

2 RESEARCH OBJECTIVES

2.1 Main criterion

The main objective is to evaluate the rate of patients without strategy failure 16 months after randomization.

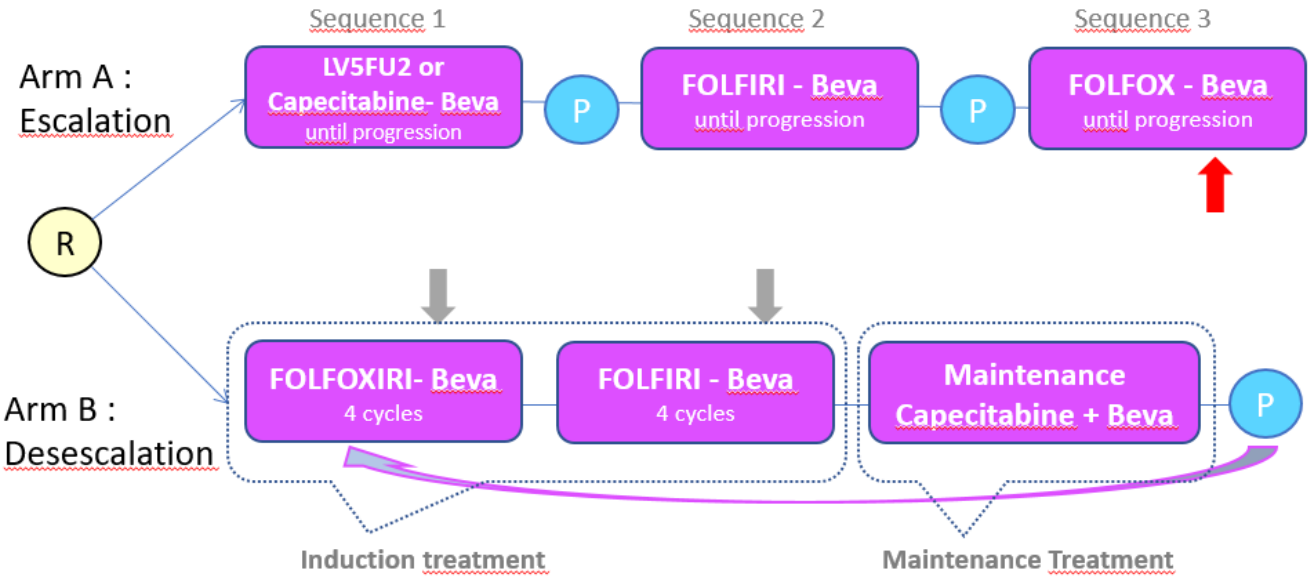
Strategy failure is defined by (Figure 1):

- Progression (defined below according to treatment strategy)* using RECIST criteria version 1.1 or
- Death (all causes) or
- Toxicity leading to permanent discontinuation of one of the chemotherapy products (oxaliplatin and/or irinotecan) or
- Patient's refusal to continue the strategy or
- Investigator's decision to discontinue strategy

***Definition of progression according to treatment strategy (two different strategies):**

- Standard strategy (escalation), progression will be considered a failure:
  - If it occurs during 1ère chemotherapy with capecitabine/LV5FU2 + bevacizumab and if 2ème chemotherapy with FOLFIRI + bevacizumab cannot be administered, or
  - if it occurs during 2ème chemotherapy with FOLFIRI + bevacizumab if 3ème chemotherapy with FOLFOX + bevacizumab cannot be administered, or
  - if it occurs during 3ème chemotherapy with FOLFOX + bevacizumab
- Experimental strategy (de-escalation), progression will be considered a failure:
  - if it occurs during the first 2 chemotherapies: modified FOLFOXIRI + bevacizumab or FOLFIRI + bevacizumab.

Figure 1



Strategy failure if : Death, progression, planned treatment could not be administrered

Primary endpoint failure if : death, progression, toxicity leading to definitive withdrawal of oxaliplatin and/or Irinotecan

Secondary criteria

The secondary objectives are as follows:

- Best response according to RECIST version 1.1 at 16 months
- Time to best response during strategy
- Time to strategy failure
- Progression-free survival at 2 years and 3 years during the
- Overall survival at 2 and 3 years
- Tolerance of both strategies
- The dose intensity of each treatment and the duration of the strategy
- Quality of life (EORTC QLQ-C30)

  The relationship between progression-free survival and BMI

2.2 Research objectives

This clinical study comprises 2 types of exploratory research

A biological collection is planned as part of the protocol cf page 28 "biological logistics".

Biological: a prospective study of the level of mutated RAS alleles in tissue (tumor) and blood (circulating DNA):

- Demonstrate the impact of RAS mutations on response to bevacizumab in mRCC.
- Prospectively determine the frequency of tumor patients with low levels of mutated RAS alleles.
- Evaluate the use of a new, highly sensitive technique for determining RAS status in blood.

- Analyze the correlation between the level of mutated RAS alleles in the primary tumor and peripheral blood.
- Analyze changes in the rate of mutated RAS alleles over time.
- Evaluate circulating VEGF (at diagnosis and every 2 cures)

Imaging :

- Assessing the relationship between PFS and tumor size at diagnosis
- Evaluate the relationship between PFS and visceral fat (measured by CT scan at inclusion)

3 SELECTION CRITERIA

3.1 Inclusion criteria

- Histologically proven metastatic colorectal cancer (on primary tumor and/or metastases)
- Non-resectable, non-pre-treated metastases
- Unmutated BRAF
- Patient considered suitable for treatment strategies
- At least one measurable target lesion > 1cm according to RECIST 1.1 (Appendix 4)
- Tumor evaluation according to RECIST, performed no more than 21 days before randomization
- Age ≥ 18 years
- WHO performance index ≤ 2 (Appendix 5)
- Life expectancy over 3 months
- Biological work-up: neutrophils ≥ 1,500 /mm^3 , platelets ≥ 100,000 /mm^3 , hemoglobin > 9 g / dL creatinine clearance > 30 mL / min (Cockcroft and Gault formula**)** (dosage modification for capecitabine if creatinine clearance < 30-50 mL / min), serum creatinine <1.5 x ULN, if dipstick proetinuria ≥ 2+, then 24h proteinuria < 1 g
- Liver workup: total bilirubin <1.5 x ULN, AST/ALT < 5 x ULN, PAL ≤ 2.5 ULN (or ≤ 5 xLNS in case of hepatic invasion)
- Women of childbearing age and men (who have sexual relations with women of childbearing age) must undertake to use effective contraception without interruption for the duration of treatment and for 6 months following the last administration.
- Signed clinical informed consent
- Patient affiliated to a social security scheme

3.2 Non-inclusion criteria

- Potentially resectable colorectal cancer, i.e. where the aim of chemotherapy is to render all metastases resectable.
- Peripheral sensory neuropathies grade >1
- Symptomatic metastases
- Symptomatic tumor in place (occulsion, hemorrhage**)**
- Active peptic ulcer, wound or bone fracture
- Inflammatory bowel disease, extensive small bowel resection
- Clinically significant active heart disease or myocardial infarction within the last 6 months.

- Hypertension not adequately controlled
- QT/QTc interval > 450 msec for men and QT/QTc interval > 470 msec for women
- K^{2+} < LIN, Mg^{2+} < LIN, Ca^{2+} < LIN
- Known DPD (Dihydropyrimidine dehydrogenase) deficiency
- Major abdominal or extra-abdominal surgery (except diagnostic biopsy) or irradiation within 4 weeks prior to the start of randomization
- Previous treatment with an anti-angiogenic agent or irinotecan
- Metastases or suspected metastases in the central nervous system
- History of malignant pathologies in the last five years, with the exception of properly treated basal cell skin carcinoma or carcinoma in situ of the uterine cervix
- Macronodular peritoneal carcinosis
- History of hemoptysis ≥ grade 2 (defined as ≥ 2.5 mL of bright red blood per episode) in the month preceding inclusion
- Known hypersensitivity to any component of bevacizumab or any of the study treatments
- Active infection requiring intravenous antibiotics at the start of treatment
- History of abdominal fistula, gastrointestinal perforation, intra-abdominal abscess or active gastrointestinal bleeding in the 6 months preceding the start of treatment.
- Pregnant or breast-feeding women
- Concurrent participation in another clinical drug study during the treatment phase and 30 days before starting study treatment
- Patient unable to undergo medical follow-up for geographical, social, psychological or legal reasons.

4 INITIAL BALANCE SHEET

After signing the consents (clinical and biological if applicable), all biological and radiological tests will be carried out at local facilities before initiating the strategy.

Patients must be informed of the possibility of preserving their germ cells. The investigator will ask the patient whether he or she wishes to preserve gametes prior to chemotherapy.

In the 21 days preceding the patient's randomization:

Morphological assessment of the tumour, with location and measurement of tumour targets according to RECIST 1.1 criteria (Appendix 4):

- Thoraco-abdomino-pelvic CT scan (TAP-CT), with and without contrast medium injection.
- If injection of iodinated contrast is contraindicated, a liver or abdominal MRI with injection and a thoracic CT scan without injection can be performed.

If bone metastases are suspected, a bone scan or X-ray will be performed; if brain metastases are suspected, a brain CT scan will be performed.

Morphological examinations should be the same throughout the patient's follow-up.

Don't forget to make an anonymized copy of this 2-month evaluation imaging in arm B (experimental) for centralized review; send to the FFCD CRGA (CD Roms or ARC FFCD).

In the 14 days preceding the patient's randomization :

Full clinical examination:

- Description of clinical signs associated with tumor disease
- Weight, height, body surface area
- Blood pressure (PAS and PAD)
- OMS general condition (appendix 5)
- ECG, or cardiology consultation if necessary

Biological check-up including :

- CBC-platelets
- Blood ionogram (Na, K, Ca), creatininemia, protidemia, albuminemia
- Liver panel including AST, ALT, PAL, GGT, total and conjugated bilirubin
- ACE, LDH
- TP and TCK
- Urine dipstick proteinuria with 24-hour proteinuria if $\geq$ 2+.
- Measurement of creatinine clearance using Cockcroft & Gault formula (Appendix 5)

RAS statutes:

The results will be recorded in the observation notebook.

Quality of life questionnaire (Appendix 6) :

QLQ-C30 questionnaire

Translational research (Appendix 3):

If the patient wishes to take part in this research and has signed the specific consent form (Appendix 2): 2 x 10 mL STRECK tubes (supplied) will be collected before administration of the 1er cycle of the 1ère chemotherapy strategy and sent at room temperature by DHL to the PRODIGE - EPIGENETEC Biological Resource Center (45 rue des Saints Pères, 75006 Paris).

- A tumor sample (tumor blocks if available, and any tumor biopsies used for diagnosis) will also be sent to the EPIGENETEC BRC.

Within 72 hours of the first chemotherapy cycle in the strategy:

- For women of childbearing age, perform a blood pregnancy test.
- Provide permanent venous access.

5 HIKING

5.1 Randomization

Randomization will be carried out by the FFCD's CRGA after the eligibility check-up and signature of the informed consent form, and after receipt of the randomization fax (Form 1 in the observation booklet), by calling 03 80 38 18 41. The CRGA is open Monday to Friday, 9am to 6pm.

For further information, please call 03 80 66 80 13.

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

If possible, the strategy should be started within 72 hours of inclusion, and within 2 weeks at most.

An observation booklet will be sent when the center opens. An observation book will be sent after each randomization.

5.2 Stratification

Patients will be randomized (1:1) using the minimization technique (Pocock and Simon (Biometrics, 1975)) according to the following stratification factors:

- Center
- WHO performance index 0/1 vs 2

6 TREATMENT

In this academic research, all drugs used in the treatment of modified FOLFOXIRI**,** FOLFIRI, FOLFOX, LV5FU2, capecitabine and bevacizumab (drugs with AMM used in their indication) will be taken from hospital stock in accordance with article L1121-16-1 of the French Public Health Code.

Please note that it is essential for investigators to refer to the AMM SPCs of the drugs used in this trial, attached in appendix 7 of the protocol, for patient management; in particular, the indications in section 4.4 "Special warnings and precautions for use", as well as the indications relating to concomitant drugs to be used with caution.

6.1 In the 48 hours preceding each cycle

Full clinical examination:

- Weight, body surface area
- Blood pressure (PAS and PAD)
- General condition WHO

Pre-chemotherapy biochemistry :

- CBC-platelets
- Creatininemia, AST and ALT
- Bilirubinemia
- Dipstick proteinuria supplemented by 24-hour proteinuria if ≥ 2+.
- Toxicity assessment according to NCI-CT version 4.0 of the previous cycle

6.2 Sch emas of administration

6.2.1 Arm A standard strategy

In the standard arm or escalation strategy, patients will receive 1ère chemotherapy based on LV5FU2 or capecitabine + bevacizumab. After progression, they will receive 2ème chemotherapy with FOLFIRI + bevacizumab. After progression, they will receive 3ème chemotherapy with FOLFOX4 + bevacizumab.

When progression occurs during 3ème chemotherapy, or 3ème CT cannot be administered, patients will be treated according to the investigator's choice.

Simplified LV5FU2 (or capecitabine) + Bevacizumab:

Bevacizumab is administered IV before chemotherapy, at a dose of 5 mg/kg over 90 min in cycle 1, then if well tolerated, over 60 min in cycle 2 and 30 min in subsequent cycles.

Folinic acid is administered as a 2-hour IV infusion at a dose of 400 mg/m² (or 200 mg/m² if Elvorine).

Bolus 5FU is administered in less than 10 minutes at 400 mg/m² (at D1).

Continuous 5FU is administered IV at a dose of 2400 mg/m² over 46 hours (D1 and D2).

Cycles last 14 days.

For this 1ère line of chemotherapy, the investigator has the option of using capecitabine instead of LV5FU2, in which case the cycle lasts 21 days. **Capecitabine** is prescribed at 2000 mg/m^2 per day, in 2 doses per os, over two weeks, followed by a one-week rest period.

FOLFIRI + Bevacizumab:

Bevacizumab is administered IV before chemotherapy, at a dose of 5 mg/kg over 90 min in cycle 1, then if well tolerated, over 60 min in cycle 2 and 30 min in subsequent cycles.

Irinotecan is administered IV at a dose of 180 mg/m² over 90 min.

Folinic acid is administered as a 2-hour IV infusion at a dose of 400 mg/m² (or 200 mg/m² if Elvorine), to be transferred to the Y at the same time as irinotecan.

Bolus 5FU is administered in less than 10 minutes at 400 mg/m² (at D1).

Continuous 5FU is administered IV at a dose of 2400 mg/m² over 46 hours (D1 and D2).

Cycles last 14 days.

FOLFOX + Bevacizumab:

Bevacizumab is administered IV before chemotherapy, at a dose of 5 mg/kg over 90 min in cycle 1, then if well tolerated, over 60 min in cycle 2 and 30 min in subsequent cycles.

Oxaliplatin is administered IV at a dose of 85 mg/m² over 120 min.

Folinic acid is administered as a 2-hour IV infusion at a dose of 400 mg/m² (or 200 mg/m² if Elvorine), to be transferred to the Y at the same time as oxaliplatin.

Bolus 5FU is administered in less than 10 minutes at 400 mg/m² (at D1).

Continuous 5FU is administered IV at a dose of 2400 mg/m² over 46 hours (D1 and D2).

Cycles last 14 days.

6.2.2 Arm B experimental strategy

In the experimental arm or de-escalation strategy, induction treatment (4 cycles of FOLFOXIRI + bevacizumab followed by 4 cycles of FOLFIRI + bevacizumab) is followed by **maintenance** treatment with capecitabine and bevacizumab until progression. After 1ère progression during maintenance treatment, the patient will be treated again with induction treatment (4 cycles of FOLFOXIRI + bevacizumab followed by 4 cycles of FOLFIRI + bevacizumab) followed by maintenance with capecitabine and bevacizumab until progression and so on.

If progression occurs during induction therapy (FOLFOXIRI + bevacizumab or FOLFIRI + bevacizumab), patients will be treated according to the investigator's choice.

Modified FOLFOXIRI + bevacizumab (4 cycles):

Bevacizumab is administered IV prior to chemotherapy, at a dose of 5 mg/kg over 90 min in cycle 1, then if well tolerated, over 60 min in cycle 2, then over 30 min in subsequent cycles.

Irinotecan is administered IV at a dose of **165 mg/m²** over 90 min.

Oxaliplatin is administered IV at a dose of 85 mg/m² over 120 min.

Continuous 5FU is administered IV at a dose of 3200 mg/m² over 46 hours (D1 and D2).

Cycles last 14 days.

GCSF is given systematically from D2 to D5 of each cycle.

Note that in this modified FOLFOXIRI regimen, irinotecan is at a dose of 165 mg/m², continuous 5-FU is at a dose of 3200 mg/m2 and bolus 5-FU is omitted.

Cycles last 14 days.

FOLFIRI + bevacizumab (4 cycles):

Bevacizumab is administered IV before chemotherapy, at a dose of 5 mg/kg over 90 min in cycle 1, then if well tolerated, over 60 min in cycle 2 and 30 min in subsequent cycles.

Irinotecan is administered IV at a dose of 180 mg/m² over 90 min.

Folinic acid is administered as a 2-hour IV infusion at a dose of 400 mg/m² (or 200 mg/m² if Elvorine), to be transferred to the Y at the same time as irinotecan.

Bolus 5FU is administered in less than 10 minutes at 400 mg/m² (at D1).

Continuous 5FU is administered IV at a dose of 2400 mg/m² over 46 hours (D1 and D2).

Cycles last 14 days.

Capecitabine + bevacizumab (maintenance treatment)

CAUTION: **Bevacizumab** should be administered IV at a dose of **7.5 mg/kg** over 90 min **every 3 weeks, when used in maintenance therapy with capecitabine.**

Capecitabine is prescribed at 2000 mg/m^2 per day, in 2 doses per os, over two weeks, followed by a week's rest. The cycle lasts 21 days.

6.3 Associated treatments

With 5FU

No systematic anti-emetic treatment

If chest pain: stop 5 FU; check ECG and cardiac enzymes

If hand-foot syndrome: moisturizing lotion, oily creams

For severe mucositis: mouthwash with bicarbonate 14 0/00, fungizone oral suspension, viscous Xylocaine® if pain and aciclovir if history of herpes.

With irinotecan

In the event of cholinergic syndrome, prescribe a subcutaneous injection of atropine (0.25 mg) immediately for curative purposes, then prophylactically 15 minutes before subsequent administrations of irinotecan®, if there are no contraindications (risk of angle-closure glaucoma, risk of urinary retention due to urethro-prostatic obstruction, paralytic ileus, achalasia, esophageal spasm, gastroesophageal reflux, toxic megacolon, pyloric stenosis, ulcerative colitis).

The patient should be discharged with a prescription for loperamide: in the event of diarrhoea, from the first liquid stool, take loperamide 2 capsules at 2 mg, then 1 capsule every 2 hours (at night, 2 capsules every 4 hours), to be continued for 12 hours after the last liquid stool, without exceeding a total of 48 hours of treatment. If diarrhea persists after 48 hours, or in the event of concomitant vomiting, fever or neutropenia, prompt hospitalization is required.

With bevacizumab

No recommended treatment; refer to treatment of side-effects for anti-hypertensive treatments or to TNCD recommendations (www.tncd.org).

For all treatments

All anti-emetic, analgesic and anti-diarrheal treatments are authorized. Loperamide is the anti-diarrheal of choice.

The use of GCSF is permitted in cases of grade 4 neutropenia, febrile neutropenia ≥ grade 3, infection with concomitant grade 3-4 neutropenia or persistent neutropenia < 1500/mm^3 after one week's deferral. If secondary prophylaxis is initiated, it will be maintained for subsequent courses.

The use of recombinant erythropoietin is authorized according to the usual recommendations.

Corticosteroids are authorized on an occasional basis, for anti-emetic purposes, but are not recommended for long-term use.

All other anti-cancer treatments are prohibited.

Preliminary radiotherapy is possible on lesions not taken as targets.

The use of a cooling helmet is permitted.

6.4 Associated treatments strictly contraindicated

With irinotecan

- St. John's wort (Irinotecan): decreased plasma levels of SN-38
- Yellow fever vaccine: risk of widespread vaccine disease

With capecitabine

- Sorivudine or related drugs (such as brivudine): risk of increased potentially fatal toxicity

With oxaliplatin :

- Drugs known to prolong the QTc interval (referenced at https://www.crediblemeds.org/) should be used with caution.

Please note that it is essential for investigators to refer to the AMM SPCs for

7 PROCESSING TIME

To correctly evaluate the 2 therapeutic strategies, it is important to respect the alternating treatment sequences of each strategy as described in the administration schedule.

The **strategy assigned at randomization will be maintained until therapeutic escape**, which differs from one strategy to another:

In the standard strategy (escalation strategy), treatment failure is defined as

- death,
- progression during 3rd-line chemotherapy (FOLFOX + bevacizumab)
- the occurrence of a toxicity requiring the definitive discontinuation of one of the chemotherapy products (redhibitory toxicity despite dose adjustment, or allergy)
- the patient's refusal to pursue the strategy
- the investigator's decision to discontinue the strategy

In the experimental strategy (de-escalation strategy), therapeutic escape is defined as :

- death,
- progression during chemotherapy with modified FOLFOXIRI + bevacizumab or FOLFIRI + bevacizumab.
- the occurrence of a toxicity requiring the definitive discontinuation of one of the chemotherapy products (redhibitory toxicity despite dose adjustment, or allergy)
- the patient's refusal to pursue the strategy
- the investigator's decision to discontinue the strategy

Permanent discontinuation of oxaliplatin and irinotecan in modified FOLFOXIRI regimens is considered therapeutic escape. It is therefore important to prevent toxicities requiring permanent discontinuation of oxaliplatin and irinotecan through dose adjustments.

However, dose adjustment of oxaliplatin or irinotecan is not considered therapeutic failure.

Permanent discontinuation of bevacizumab is not considered therapeutic failure.

If the strategy fails, patients will be treated according to the investigator's choice.

8 DOSE ADJUSTMENTS TREATMENTS

Toxicities will be assessed before each cycle by questioning, clinical examination and biology, and graded according to NCI-CTC AE version 4.0 criteria (Appendix 8 and leaflet supplied by the FFCD).

Dose adjustments are made on the basis of maximum toxicity, and if the patient presents several toxicities, adjustments are made on the basis of the highest-grade toxicity.

The decision to reduce the dose is based both on the toxicity present on the day of treatment and during the intercourse.

In the event of persistent toxicity > grade 1 on the theoretical day of treatment, treatment should be postponed for 1 or 2 weeks until recovery, before resuming treatment at the appropriate dose. Doses reduced for toxicity should not be increased again.

Oxaliplatin-specific toxicity :

- Neurotoxicity (see table 8.1)
- Cardiotoxicity

Oxaliplatin cardiotoxicity must be monitored.

In the event of QT/QTc prolongation > 500 msec: discontinue oxaliplatin therapy, with close, continuous, appropriate ECG monitoring in hospital, until a cardiologist has been consulted.

- Hypersensitivity reactions

Patients with a history of allergic reactions to other platinum-containing products should be carefully monitored. In the event of anaphylaxis, the infusion should be stopped immediately and appropriate symptomatic treatment initiated. Re-administration of oxaliplatin to patients is contraindicated. Cross-reactions, sometimes fatal, have been reported with all platinum-containing porducts.

8.1 Dose adjustments for 5FU, oxaliplatin and irinotecan

Toxicity Grade (NCI-CTC version 4.0)	5- Fluorouracil	Irinotecan or oxaliplatin (FOLFIRI or FOLFOX) Irinotecan and oxaliplatin (modified FOLFOXIRI)
Neutropenia, thrombocytopenia		
2 [a]	50% bolus reduction	No change
3 [a]	Elimination of the bolus, 25% reduction in continuous 5-FU	No change
4	Elimination of the bolus, 25% reduction in continuous 5-FU	25% discount
Febrile neutropenia [b]	Elimination of the bolus, 25% reduction in continuous 5-FU	25% discount
Diarrhea despite maximum treatment		
2	50% bolus reduction	25% discount
3	50% reduction in bolus, 25% reduction in continuous 5-FU	25% discount
4	Stopping chemotherapy	Stopping chemotherapy
Mucite		
2	50% bolus reduction	No change
3	Elimination of the bolus, 25% reduction in continuous 5-FU	No change
4	Stopping chemotherapy	Stopping chemotherapy
Vomiting		
3	No change	25% discount
4	Stopping chemotherapy	Stopping chemotherapy
Hand-foot syndrome		
2	25% reduction in continuous 5-FU	No change
3	50% bolus reduction, 50% reduction in continuous 5-FU	No change
Peripheral sensory neuropathy		
2	No change	25% reduction in oxaliplatin
3	No change	Discontinuation of oxaliplatin
Non-hematological toxicity other than alopecia		
3	25% reduction in bolus and continuous 5-FU	25% discount
4	Stopping chemotherapy	Stopping chemotherapy

[a] Discuss prescription of G-CSF if neutropenia < 1500 persists after 1 week of postponement

[b] PNN<1000 and fever >38.5°C

8.2 Capecitabine

In the event of toxicity during the capecitabine cycle, treatment should be stopped and the patient should contact a healthcare professional.

Toxicity Grade (NCI-CTC version 4.0)	Dose modification during a treatment cycle	Dosage adjustment for next cycle/dose (% of initial dosage)
Grade 1	Maintain dosage	Maintain dosage
Grade 2		
- 1st appearance	Interrupt treatment until grade 0-1 returns	100 %
- 2nd appearance		75 %
- 3rd appearance		50 %
- 4th appearance	Stop treatment permanently	Not applicable
Grade 3		
- 1st appearance	Interrupt treatment until grade 0-1 returns	75 %
- 2nd appearance		50 %
- 3rd appearance	Stop treatment permanently	Not applicable
Grade 4		
- 1st appearance	Stop treatment permanently or If the physician deems that it is in the patient's best interest to continue, discontinue treatment until grade 0-1 is restored.	50 %
- 2nd appearance	Stop treatment permanently	Not applicable

[a] Discuss prescription of G-CSF if neutropenia < 1500 persists after 1 week of postponement

[b] PNN<1000 and fever>38.5°C

8.3 Bevacizumab

Definitive discontinuation of bevacizumab due to toxicity is not a failure of the strategy. Chemotherapy will continue to be administered without bevacizumab.

ARTERIAL HYPERTENSION

- take BP after at least 5 minutes' rest
- if Systolic BP ≥ 140 mmHg and/or Diastolic BP ≥ 90 mmHg resume after a further 5 minutes' rest

Treatment of hypertension :

Grade 1 hypertension: asymptomatic, transient (< 24h) up to 150/100 mmHg

➔ No treatment and continuation of bevacizumab

Grade 2 hypertension: recurrent or persistent (> 24h) or symptomatic with diastolic BP increased by 20 mmHg or PAS/PAD > 150/100 mmHg

➔ Continuation of bevacizumab, antihypertensive monotherapy without suspension of anti-angiogenic therapy

Grade 3 hypertension: not controlled by monotherapy (or by dual therapy for patients already treated for hypertension prior to bevacizumab therapy)

➔ Discontinue bevacizumab until balanced BP is achieved

(PAS/D < 150/100 mmHg)

Grade 4: life-threatening hypertension (hypertensive crisis)

➔ Permanent discontinuation of bevacizumab

THROMBO-EMBOLIC EVENT

Permanent discontinuation of bevacizumab in the event of an arterial **thromboembolic event**

In the event of **venous thromboembolism**: suspension of bevacizumab for 2 weeks, to be resumed once effective anticoagulant therapy has been established. Permanent discontinuation of bevacizumab if life-threatening pulmonary embolism occurs.

PROTEINURY

If proteinuria ++ or +++ on pretreatment urine dipstick :

Administer bevacizumab without dose adjustment

Perform a 24-hour proteinuria test before the next cycle:

- if proteinuria ≤ 2 g/24h: administer bevacizumab without dose adjustment
- if proteinuria > 2 g/24h :
    - do not administer bevacizumab
        - repeat a 24-hour proteinuria test before the next cycle and apply the same adaptation rules
        - perform 24-hour proteinuria tests every cycle as long as proteinuria > 1g/24h

Permanent discontinuation of bevacizumab if nephrotic syndrome

INTESTINAL PERFORATION

➔ Permanent discontinuation of bevacizumab

HEMORRAGY

Grade 3 or 4

➔ Permanent discontinuation of bevacizumab

REVERSIBLE POSTERIOR ENCEPHALOPATHY SYNDROME (SEPR)

There have been rare reports of Avastin-treated patients developing signs and symptoms consistent with Reversible Posterior Encephalopathy Syndrome (RPEGS), a rare neurological disorder that can manifest itself as, among other things, seizures, headache, altered mental status, visual disturbances, cortical blindness, with or without associated hypertension. The diagnosis of RRMS requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). In patients who develop RRMS, specific treatment of symptoms, including control of hypertension, is recommended, as well as discontinuation of Avastin. The tolerability consequences of resuming Avastin treatment in patients who have developed RRMS are not known.

OSTEONECROSIS OF THE JAW

Cases of osteonecrosis of the jaw have been reported in cancer patients treated with Avastin, the majority of whom had received prior or concomitant treatment with intravenous bisphosphonates, which have a known risk of osteonecrosis of the jaw. Particular caution is advised in the case of prior or concomitant administration of Avastin with intravenous bisphosphonates. Invasive dental procedures are known to be a risk factor. A dental examination and appropriate preventive dental care should be considered before starting Avastin treatment. For patients who have previously received or are receiving intravenous bisphosphonate therapy, invasive dental procedures should be avoided if possible.

9 PATIENT MONITORING

9.1 During treatment

- Before each chemotherapy cycle:

- Complete clinical examination: weight, body surface area, general condition WHO, blood pressure
- Biological workup: CBC, platelets, ionogram (Na, K, Ca), creatinine, creatinine clearance, AST, ALT, total, free and conjugated bilirubin, proteinuria with urine dipstick and 24h proteinuria if dipstick ≥ 2+.
- Toxicity evaluation according to NCI-CTC Version 4.0 of the previous cycle
- ECG before and at the end of each intravenous oxaliplatin infusion
- If the patient has signed the specific consent form for biological research (Appendix 2): 2 x 10 mL STRECK tubes (supplied) will be **collected prior to administration of the 2ème , 5ème and 8ème** cycle and sent at room temperature by DHL to the PRODIGE - EPIGENETEC Biological Resource Center (45 rue des Saints Pères, 75006 Paris).

- Every 8 weeks:

- Clinical examination: weight, body surface area, general condition WHO, blood pressure
- Quality of Life Questionnaire QLQ-C30
- Biological tests :
  - CBC-platelets
  - Blood ionogram (Na, K, Ca), creatininemia, protidemia, albuminemia
  - Liver panel including AST, ALT, PAL, GGT, total and conjugated bilirubin
  - ACE, LDH
  - TP and TCK
  - Urine dipstick with 24-hour proteinuria if ≥ 2+.
  - Measurement of creatinine clearance using Cockcroft and Gault formula (in men: (140-age) x weight (kg)/0.814 x creatinine (µmol/L); in women: [(140-age) x weight (kg)/0.814 x creatinine (µmol/L)] x 0.85),
  - Morphological evaluation of the disease :

Do not postpone the evaluation schedule, even if cycles are postponed.

- 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.

Use the same technique as for the initial assessment.

Don't forget to make an anonymized copy of the 2-month CT scan in arm B (experimental) for centralized review; to be sent to the FFCD CRGA (CD Roms or ARC FFCD).

9.2 After discontinuation of protocol treatment

- If the protocol strategy is discontinued due to progression, clinical monitoring is maintained every 3 months for 2 years, then every 6 months for 1 year. The patient's condition and subsequent treatments are recorded in the OC.

- If treatment is stopped before tumor progression (due to toxicities or patient refusal), clinical and biological monitoring, tumor evaluation by imaging and quality of life are continued every 8 weeks. After progression, patients will be seen in consultation every 3 months for 2 years, then every 6 months for 1 year. The patient's condition and subsequent treatments will be recorded in the OC.

10 ORGANIC LOGISTICS

All patients randomized in the PRODIGE 45 - HIGH-LIGHT study and having signed the specific consent form for this translational research (prospective study of the rate of mutated RAS alleles at tissue level (tumor) and at blood level (circulating DNA) in metastatic colorectal cancer as part of the high-light study) are eligible for inclusion.

Determining tumor mutation status

There will be a standard RAS status determination in each hospital.

Subsequent confirmation of RAS (KRAS and NRAS) status will be carried out centrally (pyrosequencing, Poitiers University Hospital) from the collection of tumor blocks.

The tumour blocks (tumour blocks if available, and any tumour biopsies used for diagnosis) will be sent to the EPIGENETEC BRC:

EPIGENETEC - INSERM Unit U775
45 rue des Sts Pères
75006 PARIS

Determining mutation status in blood

For centralized analysis of circulating KRAS and mutant NRAS DNA, blood samples will be taken prior to chemotherapy infusion in cycles 1, 2, 5 and 8, i.e. a total of 4 samples for each patient. These samples should be taken on STRECK tubes supplied, in 2 x 10 mL tubes.

The tubes will be transported to the EPIGENETEC BRC via a courier immediately after sampling.

11 MANAGEMENT OF SERIOUS ADVERSE EVENTS (EIG)

Safety will be assessed by evaluating patients' general and clinical condition, and by recording events occurring between visits during consultations, and by regular blood tests. Toxicities will be assessed using the NCI-CTC-AE version 4.0 toxicity scale, and collected in the observation notebook (see Appendix 8).

In the event of an emergency, the patient, the patient's family or the patient's doctor should call the investigator to inform him of the event.

11.1 Definitions

Adverse Event (AE)

An adverse event is a noxious occurrence in a person undergoing biomedical research, whether or not it is related to the research or to the research product.

Serious adverse event (SAE)

A serious adverse event is any event that meets at least one of the following criteria:

- Resulting in death,

- Life-threatening,

- Resulting in hospitalization or prolongation of hospitalization,

- Causing permanent disability or severe temporary incapacity,

- Causing birth defects, fetal malformation or abortion,

- Medically significant

The terms disability and incapacity refer to any temporary or permanent, clinically significant physical or mental handicap affecting the patient's physical activity and/or quality of life.

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 place the patient at risk and require medical intervention to prevent an outcome corresponding to one of the above-mentioned severity criteria (e.g. overdoses, second cancers, pregnancies and new events may be considered medically significant).

Pregnancy is a criterion for non-inclusion in this trial, and contraceptive measures must be taken throughout treatment and up to 6 months after discontinuation. However, if pregnancy is discovered in an enrolled patient after inclusion, she must be excluded from the trial, and the sponsor must be informed without delay via the serious adverse event notification form (no severity criteria will be ticked). The patient must be followed until the end of the pregnancy, and this outcome, whatever it may be, must be reported to the sponsor.

Similarly, if a pregnancy occurs in the partner of a patient included in the trial, the sponsor must be informed in the same way and will try, as far as possible, to follow the pregnancy to term.

Undesirable effect

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

Unexpected Serious Adverse Effect

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

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 CTC-AE version 4.0 classification extract (appendix 8). 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 activities

- Very severe (grade 4): requires resuscitative measures / life-threatening

- Death (grade 5).

Causal relationship

Related: an event is said to be related when a causal relationship between the event and the product under study can reasonably be suspected.

Unrelated: an event is said to be unrelated when a causal relationship between the event and the product under study cannot reasonably be suspected.

Doubtful: causality is said to be "doubtful" when there is doubt about the causal relationship between the event and the product under study (the relationship can then be neither formally excluded nor formally affirmed).

Developer's liability

On receipt of the investigator's report of a serious adverse event, the sponsor must issue an opinion on the causal relationship between the serious adverse event and the study product(s).

If the serious adverse event is linked by the investigator and/or sponsor to one of the products under study (i.e. a serious adverse event), the investigator and/or sponsor must establish whether the event was expected or unexpected.

In the case of an unexpected serious adverse event, or a new development, the sponsor draws up an initial report which is sent to the ANSM, the CPP and the EMA (via EudraVigilance) within 7 days in the case of death or life-threatening event, otherwise within 15 days.

If it is an expected serious adverse event, it will be collated for the purposes of the half-yearly and annual safety reports.

11.2 Events not to be considered serious

Disease progression should not be considered as a SAE. On the other hand, events potentially linked to the progression of the disease but which may be secondary to 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, i.e. :

- Hospitalization or surgery specifically related to the treatment of the disease

- Hospitalization to simplify study treatments or procedures

In this test, the reference documents will be :

- For 5FU, the Summary of Product Characteristics for Fluorouracil Ebewe® 50 mg/mL (Appendix 7)
- For folinic acid, the Summary of Product Characteristics for Elvorine® (Appendix 7)
- For oxaliplatin, the Summary of Product Characteristics for Eloxatine® (Appendix 7)
- For irinotecan, the Summary of Product Characteristics for Campto® (Appendix 7)
- For capecitabine, the Summary of Product Characteristics for Xeloda® (Appendix 7)
- For bevacizumab, the Avastin® Summary of Product Characteristics (Appendix 7)

The PCR versions used to define whether a product is expected or unexpected are those in force at the time of analysis.

NB: for 5-fluorouracil, venous thromboembolic events are considered as expected, although not listed in the RCP.

11.3 Procedure

The investigator informs the sponsor of all Serious Adverse Events (expected and unexpected), whether attributable to the research or not, which 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 must be reported without time limit.

The report is made by faxing the "notification of a serious adverse event" form, documented as accurately as possible, dated and signed, within 24 working hours of the SAE's detection, to the FFCD's Centre de Randomisation Gestion Analyse (CRGA) by fax (03 80 38 18 41).

The investigator is responsible for the appropriate medical follow-up of patients until resolution or stabilization of the effect, or until the patient's death. This may sometimes involve extending follow-up beyond the trial patient's protocol monitoring period.

He/she transmits the additional information to the sponsor using an SAE reporting form (ticking the Follow-up n° X box to specify that this is a follow-up report and not an initial report) within 24 hours of obtaining 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.

12 STATISTICAL ANALYSIS

12.1 Judging criteria

Primary endpoint

The primary endpoint is the rate of patients without strategy failure 16 months after randomization.

Strategy failure is defined by (see figure 1):

- Progression (under certain conditions) using RECIST criteria version 1.1 or
- Deaths (all causes) or
- Toxicity leading to permanent discontinuation of one of the chemotherapy products (oxaliplatin and/or irinotecan) or
- Patient's refusal to continue the strategy or
- Investigator's decision to discontinue strategy

Progression has a different definition depending on the strategy, because the two strategies are different:

In the standard strategy (escalation), progression is considered a failure:

- If it occurs during 1ère chemotherapy (LV5FU2 + bevacizumab) and if 2ème chemotherapy (FOLFIRI + bevacizumab) cannot be administered, or
- if it occurs during 2ème chemotherapy (FOLFIRI + bevacizumab) and if bevacizumab) and if 3ème chemotherapy (FOLFOX + bevacizumab) cannot be administered e or
- if it occurs during 3ème chemotherapy.

In the experimental strategy (de-escalation), a progression is considered a failure:

- if it occurs during intensive chemotherapy (modified FOLFOXIRI + bevacizumab) or if it occurs during chemotherapy with FOLFIRI + bevacizumab

Secondary endpoints

The best response according to RECIST version 1.1 at 16 months will be assessed on scans performed during the strategy.

The time to best response will be the time between the date of randomization and the date of the first best response scan to the strategy.

Time to strategy failure will be the time between the date of randomization and the date of strategy failure (according to the definition of the primary endpoint).

For progression-free survival, the time between the date of randomization and the date of the first radiological progression or death (from any cause) will be calculated. Patients alive without progression will be censored at the date of their last news.

For overall survival, the time between the date of randomization and the date of death (from all causes) will be calculated. Living patients will be censored at the date of their last news.

The tolerability of both strategies will be evaluated according to reported toxicities (NCI-CTC version 4.0) and their grade. The following events of particular interest will also be described: hypertension, proteinuria, gastrointestinal perforation, abscesses and fistulas, wound healing complications, hemorrhages, arterial and venous

thromboembolic events, posterior reversible encephalopathy syndrome, congestive heart failure, non-gastrointestinal fistulas and abscesses.

The dose intensity of each treatment and the duration of the strategy will be described. The duration of the strategy will be calculated as the time between the date of the first course of treatment and Day 1 of the last course (+14 days if the patient is receiving 5FU IV or +21 days if the patient is receiving capecitabine).

Quality of life (QLQ-C30 EORTC v3.0 questionnaire) will be studied descriptively. Time to deterioration in quality of life will be studied.

12.2 Calculating the number of subjects required

The clinical hypotheses for the study design are as follows:

H_0 : A rate of 40% of patients alive and without strategy failure at 16 months is not interesting.

H_1 : A live patient rate without strategy failure at 16 months of 55% is expected.

With an α risk (one-sided) of 5% for a power of 80.85%, using the exact binomial method (15) (R software), 75 patients will be randomized to each strategy.

Taking into account that 10% of patients will not be evaluable for the mITT population, 84 patients per strategy will be randomized according to the 1:1 ratio.

The conclusion of the study will be based solely on the experimental strategy as defined below and on the first 75 evaluable patients:

If 38 or more patients do not fail the strategy at 16 months, the strategy is considered effective.

12.3 Statistical analysis plan

12.3.1 Analysis populations

ITT population (ITT): All patients included in the study, regardless of inclusion or non-inclusion criteria, and analyzed according to the strategy assigned by randomization.

Modified ITT population (mITT): All patients in the ITT population who received at least one dose of treatment (regardless of dose and treatment) and who underwent imaging assessment during the strategy.

Per-protocol population (PP): All patients in the ITT population who have had at least one dose of treatment (regardless of dose and treatment) and who have had an imaging evaluation during the strategy and have no major protocol deviations.

Population Tolerance (PT): All patients included in the study who received at least one dose of treatment (whatever the dose and treatment). The analysis will be performed according to the strategy actually used.

Analysis of the primary and secondary efficacy endpoints will be performed in ITTm and ITT population.

The primary endpoint and efficacy criteria will also be assessed in the per-protocol (PP) population.

Tolerance criteria will be analyzed in the tolerance population (TP).

12.3.2 Evaluation of criteria

General considerations

All analyses will be performed using SAS software version 9.4 or higher or STATA V10 or higher. A statistical analysis plan will be drawn up before the database is frozen. Any subsequent changes to this analysis plan must be detailed, justified and commented on in an updated version. Such modifications may concern additional exploratory analyses not initially envisaged.

Continuous variables are described using mean, standard deviation, median, inter-quartile range, minimum and maximum. Categorical variables are described using frequencies and percentages.

Demographic and clinical characteristics at inclusion will be described for the ITT population.

Evaluation of efficacy criteria (mITT and ITT):

The rate of patients without strategy failure at 16 months will be calculated on the basis of the investigator's assessment at 16 months +/- 30 days. It will be described using a percentage and a one-sided 95% confidence interval.

Survival and time will be estimated using the Kaplan-Meier 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 Kaplan-Meier" method.

The best response to treatment will be described by strategy, as will the time to best response and the time to strategy failure.

QLQ-C30 scores will be described by strategy at inclusion and during follow-up. Based on the overall score, the time to definitive deterioration, defined as the time between randomization and the date of a decrease of more than 5 points (compared with inclusion) without improvement, will also be analyzed by the Kaplan-Meier method.

Evaluation of tolerance criteria (PT) :

The duration of treatment for each chemotherapy and the total duration of the strategy will be described using descriptive statistics. The dose intensity of each treatment will be described.

Toxicities will be described, by strategy, and by grade. In addition, the following events of particular interest will also be described: hypertension, proteinuria, gastrointestinal perforation, abscesses and fistulas, wound healing complications, bleeding, arterial thromboembolic events, venous thromboembolic events, posterior reversible encephalopathy syndrome, congestive heart failure, fistulas and non-gastrointestinal abscesses.

12.4 Study committees

12.4.1 Independent Committee

An independent monitoring committee will be set up, including at least 2 gastroenterologists/oncologists, a statistician and a pharmacovigilance expert. The independent committee will assess safety data (toxicities and SAEs) on a regular basis. It may also be called upon at any time during the study, should the FFCD deem it necessary. Their functions will be described in the independent monitoring committee charter.

The Chairman of the Independent Committee will forward his recommendations to the Chairman of the Steering Committee.

12.4.2 Board of Directors

A steering committee will be set up, chaired by the main coordinator. This committee will include a UNICANCER representative, a representative of the sponsor, the FFCD project manager, the FFCD statistician and the chairman of the Biological Research Committee. Its mission will be, among other things, to make decisions relating to the management of the research (amendment, premature closure if necessary, etc.). This committee will meet as often as necessary throughout the study.

12.4.3 Biological Committee

A Biological Research Committee will be set up to manage and bank blood and tumor samples. It will identify relevant biological prognostic and predictive factors, as well as relevant polymorphisms to be tested. It will organize analyses with selected laboratories. This committee will include the members of the study's steering committee; its

chairman will be the head of the EPIGENETEC CRB, Prof. Pierre Laurent-Puig.

This committee will meet regularly and report on its biological research projects to the steering committee and the sponsor.

13 LEGAL AND ETHICAL ASPECTS

STUDY SPONSOR

The study sponsor is the Fédération Francophone de Cancérologie Digestive (FFCD). The study has been registered under EudraCT number 2016-001225-13.

CURRENT LEGISLATION

This test will be carried out in accordance with the new European Directive 2001/20/EC.

LIABILITY INSURANCE

Insurance was taken out by the promoter on 17/03/2016 under number 137681, in accordance with article L 1121-10 of the public health code (Appendix 10).

REQUEST FOR AUTHORIZATION FROM CPP AND ANSM

This protocol received the favorable opinion of the CPP (Comité de protection des personnes) Sud Est I on 11/05/2016 (Appendix 11).

This protocol received authorization from the ANSM (Agence Nationale de Sécurité du médicament et des produits de santé) on 18/05/2016 (Appendix 12).

OBTAINING THE PATIENT'S CONSENT

The investigator undertakes to obtain the patient's written clinical and biological consent (information sheets and consent forms in Appendices 1 and 2) before the patient is enrolled in the study. The investigator must keep a copy of these consents for 15 years, for presentation to the regulatory authorities in the event of inspection. The original must be given to the patient.

In accordance with the recommendations of the Cancer Plan (Measure 5.4), this document has been submitted to the Patients' Committee for Clinical Research (CPRC) of the Ligue Nationale Contre le Cancer.

HOSPITAL MANAGEMENT INFORMATION AND RESEARCH AGREEMENT

Prior to setting up the study, hospital management will be informed by the promoter of the investigator's interest in participating in the trial.

A research agreement will be drawn up between the administrator of the investigating center and the sponsor.

DATA ARCHIVING

Records will remain confidential and may only be consulted under the responsibility of the doctors in charge of the patients. The promoter and, in the event of an inspection, the health authorities 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.

IT SUPPORT

In accordance with the French Data Protection Act no. 78-17 of January 6, 1978, as amended by the Act of August 9, 2004, trial data will be stored in a computer database at the FFCD's Randomization and Analysis Management Center, with the exception of information relating to patient identity.

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 THE AUTHORITIES

The investigator accepts in advance that the files of included patients may be consulted by a person mandated by the FFCD and/or the health authorities to carry out an audit. On-site file visits, scheduled with the investigator's agreement, may take place during or after the trial inclusion period.

This protocol will be monitored by the FFCD's mobile ARCs.

14 PUBLICATION

PRODIGE publication rules will be applied (Appendix 9). Publications follow ICMJE recommendations (16).

15 REFERENCES

1- Koopman M, Simkens LH, Ten Tije AJ et al. Maintenance treatment with capecitabine and bevacizumab versus observation after induction treatment with chemotherapy and bevacizumab in metastatic colorectal cancer: The phase III CAIRO3 study of the Dutch Colorectal Cancer Group. J Clin Oncol;31 (suppl, A 3502)

2- Chibaudel B, Maindrault-Goebel F, Lledo G et al. Can chemotherapy be discontinued in unresectable metastatic colorectal cancer? The GERCOR OPTIMOX2 Study. J Clin Oncol 2009;27:5727-33

3- Falcone A, Cremolini C, Masi G, et al. **Modified** FOLFOXIRI/bevacizumab (bev) versus FOLFIRI/bev as first-line treatment in unresectable metastatic colorectal cancer (mCRC) patients (pts): Results of the phase III TRIBE trial by GONO group. J Clin Oncol 31, 2013 (suppl; abstr 3505)

4- Hurwitz H, Fehrenbacher L, Novotny W et al. Bevacizumab plus Irinotecan, Fluorouracil, and Leucovorin for Metastatic Colorectal Cancer. N Engl J Med 2004;350:2335-42

5- Lenz H, Niedzwiecki D, Innocenti F et al. CALGB/SWOG 80405: PHASE III trial of irinotecan/5-FU/leucovorin (FOLFIRI) or oxaliplatin/5-FU/leucovorin (mFOLFOX6) with bevacizumab (BV) or cetuximab. Annals of Oncology (2014) 25 (5): 1-41

6- Saunders MP et al. Efficacy and safety according to age subgroups in AVEX, a randomized phase III trial of bevacizumab in combination with capecitabine for the first-line treatment of elderly patients with metastatic colorectal cancer. J Clin Oncol 2013 (suppl, A 3521)

7- Hegewisch-Becker S, Graeven U, Lerchenmüller C et al. Maintenance strategy with fluoropyrimidines (FP) plus bevacizumab (Bev), Bev alone or no treatment, following a 24-week first-line induction with FP, oxaliplatin (Ox) and Bev for patients with metastatic colorectal cancer: Mature data and subgroup analysis of the AIO KRK 0207 phase III study. Annals of Oncology (2014) 25 (suppl_4)

8- Aparicio T, Bennouna J, Le Malicot et al. Interim analysis of PRODIGE 9, a randomized phase III trial comparing no treatment to bevacizumab maintenance during chemotherapy-free intervals in metastatic colorectal cancer. Annals of Oncology (2014) 25 (suppl_4)

9- Bennouna J, Sastre J, Arnold D et al. Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial. Lancet Oncol 2013 ;14 :29-37

10- Masi G, Loupakis F, Salvatore L et al. Second-line chemotherapy (CT) with or without bevacizumab (BV) in metastatic colorectal cancer (mCRC) patients (pts) who progressed to a first-line treatment containing BV: Updated results of the phase III "BEBYP" trial by the Gruppo Oncologico Nord Ovest (GONO). J Clin Oncol 2013 ;31, (Suppl15, A3615)

11- Van Cutsem E, Tabernero J, Lakomy R et al. Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. J Clin Oncol 2012;30:3499-3506

12- Ducreux M, Castaing M, Etienne PL et al. Strategic trial of chemotherapy for metastatic colorectal cancer (FFCD 2000-05 study). Preliminary results. Gastroenterol Clin Biol 2008 ;32 :A25

13- Koopman M, Antonini NF, Douma J et al. Sequential versus combination chemotherapy with Capecitabine, Irinotecan and Oxaliplatin in advanced colorectal cancer (CAIRO): a phase III randomized controlled trial. Lancet 2007 ;370 :135-42

14- Seymour MT, Maughan TS, Ledermann JA et al. Different strategies of sequential and combination chemotherapy for patients with poor prognosis advanced colorectal cancer (MRC FOCUS): a phase III randomized controlled trial. Lancet 2007;370:143-52

15- A'Hern R. P., Sample size tables for exact single-stage phase II designs. Statistics in medicine 2001; 20:859 - 866

16- Recommendations for the Conduct, Reporting, Editing, and

Publication of Scholarly Work in Medical Journals. ICMJE recommendations December 2014