UNICANCER Group Tumour: UNICANCER GI

Protocol N°: UC-1110/0906

Clinical Trial N°: NCT01442649

UNICANCER GastroIntestinal Group

PRODIGE 18 - ACCORD 22

Phase II, multicentric randomized trial, evaluating the efficacy of fluoropyrimidine-based standard chemotherapy, associated to either cetuximab or bevacizumab, in KRAS wild-type metastatic colorectal cancer patients with progressive disease after receiving first-line treatment with bevacizumab

Version n°6 03/06/2014
Accepted by the CPP Ouest III
And submitted for information to the ANSM

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CLINICAL TRIAL AUTHORIZATION FOR PROTOCOL PRODIGE 18-ACCORD 22

Phase II, multicentric randomized trial, evaluating the efficacy of fluoropyrimidine-based standard chemotherapy, associated to either cetuximab or bevacizumab, in KRAS wild-type metastatic colorectal cancer patients with progressive disease after receiving first-line treatment with bevacizumab

COMPETENT AUTHORITY ANSM	**Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM)**	**Approval date : 24/08/2010**
		Réf. ANSM A100791-11
ETHIC COMMITTEE	**Name of the EC : Ouest III**	**Decision date : 30/08/2010**
		Réf. CPP 10-07-15

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SYNOPSIS – PRODIGE 18 - ACCORD 22

A) TRIAL IDENTIFICATION	
UNICANCER – PROTOCOL CODE NUMBER: UC-1110/0906 **VERSION ET DATE : *VERSION N°6 03/06/2014***	
TRIAL TITLE: Phase II, multicentric randomized trial, evaluating the efficacy of fluoropyrimidine-based standard chemotherapy, associated to either cetuximab or bevacizumab, in KRAS wild-type metastatic colorectal cancer patients with progressive disease after receiving first-line treatment with bevacizumab	
ABBREVIATED TITLE: Prodige 18 – Accord 22 (A UNICANCER GI trial)	
COORDINATING INVESTIGATOR: Prof Jaafar BENNOUNA Address: Institut de Cancérologie de l'Ouest - site René Gauducheau; Bvd Jacques Monod 44805 SAINT HERBLAIN Tel: 02 40 67 99 78 Fax: 02 40 67 97 05 E-mail: jaafar.bennouna@ico.unicancer	
NUMBER OF CENTRES: 30	NUMBER OF PATIENTS: 132
EUDRACT N° 2009-012942-22	NCT01442649

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C) TRIAL GENERAL INFORMATION
INDICATION: Treatment of wild-type RAS (KRAS and NRAS) metastatic colorectal cancer patients after failure of a first-line treatment with bevacizumab.
TRIAL DESCRIPTION/DESIGN: A multicentre, randomised, open-label phase II study was designed to evaluate the efficacy and safety of bevacizumab or cetuximab associated with a standard fluoropyrimidine-based chemotherapy for treating patients with wild-type RAS (KRAS and NRAS) metastatic colorectal cancer after first-line treatment with bevacizumab.

PRIMARY OBJECTIVE:

To evaluate the efficacy in terms of PFS at 4 months

SECONDARY OBJECTIVES:

- To evaluate the efficacy in terms of:
  - ✓ Objective response rate (OR)
  - ✓ PFS
  - ✓ OS
  - ✓ OS from the date of the first-line chemotherapy used on the metastatic disease
- To evaluate the treatment tolerance
- To evaluate the quality of life (QoL)
- To study the potential predictive factors

EXPLORATORY OBJECTIVES:

- To identify predictive factors for the response to anti-EGFR and anti VEGF treatments

DIAGNOSIS AND INCLUSION CRITERIA:

1. Histologically or cytologically proven colorectal adenocarcinoma expressing wild-type RAS (KRAS and NRAS).
2. Progressive metastatic disease after first-line treatment with only one previous chemotherapy based on 5-FU (IV or per os) with irinotecan or oxaliplatin associated with bevacizumab.
3. Prior fluoropyrimidine-based adjuvant chemotherapy (for the primary tumor) with oxaliplatin is allowed if the time interval between the end of this chemotherapy and the beginning of the first-line metastatic treatment is ≥6 months.
4. Measurable disease (at least one measurable metastatic lesion by RECIST V1.1 criteria, with lesion not located in a previous field of radiation).
5. Previous radiotherapy is authorized if discontinued ≥15 days prior to randomization and if the measurable metastatic lesions are outside the radiation area.
6. Sites of disease evaluated within 28 days prior to randomization with thoracic-abdominal-pelvic CT scan (or abdominal-pelvic MRI and chest X-ray)
7. Age ≥18 years
8. Patient with ECOG 0 or 1
9. Life expectancy ≥12 weeks
10. Hematologic function: polynuclear neutrophils ≥ $1.5.10^9$/L; platelets ≥100.10^9/L; haemoglobin ≥9 g/dL
11. Hepatic function: transaminases ≤2.5 times upper limit of normal (ULN) (≤5 ULN in case of hepatic metastases), alkaline phosphatases ≤2.5 x ULN (≤5 ULN in case of hepatic metastases), total bilirubin ≤1.5 x ULN
12. Renal function: creatinemia ≤1.5 x ULN; creatinine clearance ≥50 mL/min (Cockcroft and Gault); urine test strip <+2. If proteinuria is ≥+2 at inclusion, the serum urea test must be redone and show proteinuria ≤1 g/L within 24 h)
13. Patients having completed the EORTC QLQ-C30 quality of life form
14. Negative pregnancy test for women of child-bearing age
15. Information given to the patient and signed informed consent
16. Public Health insurance coverage

NON-INCLUSION CRITERIA:

The patients included in this study should not meet any of the following non-inclusion criteria:

1. Known meningeal or brain metastases
2. Patient previously treated with an anti-EGFR
3. Specific contraindication or known hypersensitivity to one of the study treatments
4. Patients who received a dose de-escalation scheme e.g.LV5FU bevacizumab followed by FOLFOX or FOLFIRI with bevacizumab.
5. Patient with known allergy or hypersensitivity to monoclonal antibodies (bevacizumab, cetuximab), or to Chinese hamster ovarian cell products or any other humanized or recombined antibodies or any other chemotherapies under study, and their excipients.
6. Clinically significant coronaries affection or myocardial infarction within 6 months prior to inclusion.
7. Peripheral neuropathy of grade >1 (CTCAE scale version 4.0).
8. Known dihydropyrimidine dehydrogenase (DPD) deficiency.
9. Acute intestinal obstruction or sub-obstruction, history of inflammatory intestinal disease or extended resection of the small intestine. Presence of a colic prosthesis.
10. Unhealed wound, active gastric or duodenal ulcer, or bone fracture
11. History of abdominal fistulas, trachea-oesophageal fistulas or any other grade 4, gastro-intestinal perforations or non-gastrointestinal fistulas or intra-abdominal abscesses during the 6 months before inclusion.
12. Uncontrolled arterial hypertension (systolic pressure >150 mmHg and/or diastolic pressure >100 mmHg with and without antihypertensive medication. Patients with high hypertension are eligible if antihypertensive medication lowers their arterial pressure to the level specified by the inclusion criterion.
13. History of hypertensive crisis or hypertensive encephalopathy
14. Thromboembolic event in the 6 months before inclusion (e.g. transitory ischemic stroke, stroke, subarachnoid haemorrhage) except peripheral deep vein thrombosis treated with anticoagulants
15. Other concomitant malignancy or history of cancer (except in situ carcinoma of the cervix, or non-melanoma skin cancer, treated with curative intent treatment) except if considered in complete remission for at least 5 years before randomization.
16. Existence of any other pathology, metabolic problem, anomaly during the clinical examination or biological anomaly which may reasonable suspect an underlying pathology which would contra-indicate the use of the study medication or any other risk of complication related to the treatment.
17. Any treatment including an experimental drug, or participation in another clinical trial within 28 days before randomisation.
18. Pregnant women, or women who could possibly be pregnant (or who expect to fall pregnant within 6 months of the end of treatment), or who are breast feeding are not eligible.
19. Men and women of child-bearing age who do not accept to use a highly effective contraceptive (as per currently acceptable institutional standards) or abstinence during the study and for the 6 months after the last administration of the study treatments.
20. Persons deprived of liberty or under guardianship.
21. Psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule.

PRIMARY ENDPOINT:

Progression-free survival (PFS) at 4 months

PFS is defined as the time from randomization to progression (RECIST v1.1) or death

SECONDARY ENDPOINTS:

- Objective response rate (OR):
  The objective response rate is defined as the occurrence of a complete response (CR) or a partial responses (PR) according to RECIST v1.1 between date of randomization and date of end of treatment. It will be evaluated by the investigator with RECIST v1.1 every 6 weeks until disease progression.
- PFS:
  Progression-free survival is defined as the time from randomization to progression (RECIST v1.1 criteria) or death. Patients alive without progression will be censored at the last follow-up.
- Overall survival (OS):
  OS is defined as the time from randomization to death any cause or last follow-up (censored data).
- OS from the date of the first-line chemotherapy used on the metastatic disease:
  OS from the date of the first-line chemotherapy used on the metastatic disease is defined as the time from the first day of the first-line chemotherapy used on the metastatic disease to death any cause or last follow-up news (censored data).
- Treatment tolerance:
  Tolerance of the treatment will be based on toxicities of evaluated products by clinical and biological measurements (NCI CTCAE V4), except for peripheral neuropathy toxicity (Lévi scale).
- Quality of life:
  Quality of life will be evaluated with the EORTC QLQ-C30.

RANDOMISATION

Randomisation shall be carried out by minimisation and stratified on:

- 1st-line chemotherapy: chemotherapy based on fluoropyrimidine/oxaliplatin versus fluoropyrimidine/irinotecan
- Progression-free survival of the 1st-line treatment ≤9 months versus >9 months
- The centre

D) INVESTIGATIONAL MEDICINAL PRODUCTS

Product names and administration

Drug name (INN)	Registered name	Pharmaceutical form	Administration route	Posology
bevacizumab	Avastin®	Solution to dilute for perfusion at a concentration of 25 mg/mL. Vials of 4 and 16 mL.	IV	5 mg/kg every 2 weeks
cetuximab	Erbitux®	Solution for perfusion 5 mg/mL. Vials of 20 or 100 mL	IV	500 mg/m^2 every 2 weeks
5-fluorouracil		Powder for preparing an injectable solution	IV	400 mg/m² bolus, and 2400 mg/m² infusion over 46 h starting on D1 of a 14 day cycle
folinic acid		Powder for preparing an injectable solution	IV	200 mg/m² of the enantiomeric (levorotary) form or 400 mg/m² of the racemic mixture

oxaliplatin	Eloxatine®	Powder or solution for perfusion	IV	85 mg/m² on D1 of a 14 day cycle
irinotecan	Campto®	Solution to dilute for perfusion	IV	180 mg/m² on D1 of a 14 day cycle

THERAPEUTIC REGIMENS:

- Bevacizumab (Arm A)

Bevacizumab (5 mg/kg IV every 14 days) and standard fluoropyrimidine-based chemotherapy.

- Cetuximab (Arm B)

Cetuximab (500 mg/m^2 IV every 14 days) and standard fluoropyrimidine-based chemotherapy.

Associated with standard fluoropyrimidine-based chemotherapy (either mFOLFOX6 or FOLFIRI).

✓ mFOLFOX6

Oxaliplatin: 85 mg/m^2 in 120 min IV on D1; folinic acid: 400 mg/m² (racemic) (or 200 mg/m² if L-folinic acid) in 2 h IV on D1 (simultaneously with oxaliplatin using a Y tube). Then 5-fluoro-uracil: 400 mg/m² bolus IV on D1 and then 5-fluoro-uracil: 2400 mg/m² perfusion IV over 46 h

✓ FOLFIRI

Irinotecan: 180 mg/m^2 in 90 min IV on D1. Folinic acid: 400 mg/m² (racemic) (or 200 mg/m² if L-folinic acid) in 2 h IV on D1 (simultaneously with irinotecan using a Y tube). Then 5-fluoro-uracil: 400 mg/m² bolus IV on D1 then 5-fluoro-uracil: 2400 mg/m² perfusion IV over 46 h.

TREATMENT DURATION:

- Patients were treated until disease progression.
- In the case of discontinuation of chemotherapy due to toxicity, the targeted therapy was continued until progression.

The treatment shall be started within 7 days after randomisation. The treatment duration in this study is envisaged until disease progression or unacceptable toxicity.

In the event of definitive discontinuation of chemotherapy for other reason then progression, bevacizumab and/or cetuximab shall be continued until disease progression except in the event of unacceptable toxicity, or patient or investigator decision.

The choice of post-progression treatment shall be left up to the investigator. Patients whose disease progression has been documented shall cease to receive the study treatment and shall be the subject of follow-up until the time of their death.

POSOLOGY : Cf. therapeutic scheme

TREATMENT DURATION : until progression

E) STATISTICAL ANALYSIS

REQUIRED NUMBER OF PATIENTS:

The primary objective of the study is the Progression-Free Survival (PFS). All patients should have at least 4 months of follow-up.

According to the Simon two-stage method (Optimax) with a 5% unilateral alpha error risk, a 90% power and the following hypotheses:

H0: A 30% Progression-Free Survival rate at 4 months is not of interest.
H1: A 50% Progression-Free Survival rate at 4 months is expected.

It is required to include 59 patients in each of the arms (total 118 patients).

A total of 132 patients shall therefore be included to obtain 118 patients suitable for analysis. In order to account for those lost to follow-up and non evaluable for primary objective, 10% additional patients should be included, 14 additional patient will be included.

INTERIM ANALYSIS :

At the end of stage 1, after the inclusion of 20 initial patients having at least 4 months of follow-up in each arm:

- If 6 or less than 6 living progression-free patients are observed after 4 months of follow-up (30.0%), the PFS rate being ≤ 30%, the treatment shall be deemed not to be of interest for the evaluation of this association of treatments and the inclusion for this arm shall be discontinued.
- If 7 or less more than 7 living progression-free patients are observed after 4 months, the inclusion for this arm shall be continued with 39 patients.

The power is 94%.

At the end of stage 2, after the inclusion of 59 patients having at least 4 months of follow-up in each arm:

- If 23 or less than 23 living progression-free patients are observed after 4 months of follow-up (39.0%), the PFS rate ≤ 30%, the treatment shall be deemed not to be of interest for the evaluation of this association of treatments.
- If 24 or more than 24 living progression-free patients are observed after 4 months of follow-up (40.7%), the PFS rate >30%, the treatment shall be deemed to be of interest for the evaluation of this association of treatments.

The power is 96% with an alpha error risk of 4.5%.

The total power is 90.2%, and the alpha error risk 4.5%.

During the analysis of the first stage, the inclusions shall not be stopped as the treatment administered is a standard in the care of this disease.

11.2 Statistical analysis

No statistical comparison is envisaged between the arms in the randomised phase II study

The statistical analysis shall be conducted on an intention-to-treat basis. The intention-to-treat (ITT) population is defined as the set of included patients having received the complete study treatment or not.
The tolerance analysis population is defined as the set of included patients having received at least one administration of one of the study medicines.

The characteristics at inclusion of the total population (e.g. patients enrolled in the study) shall be described using descriptive statistics:

Frequency and percentage for categorical and ordinal variables,
Or
Mean (stable disease); median (Min-Max) for continuous and ordinal variables.

The PFS rate at 4 months, representing the percentage of the total population (ITT) with a 95% confidence interval (CI) in each arm, shall be analysed according to the Simon method. The number and type of progressions shall be reported in each arm.

The survival estimation shall be described with a median confidence interval (95%CI) with the Kaplan-Meier method.
The median follow-up shall be calculated according to the so-called "reverse Kaplan Meier" method for each of the arms with its 95% confidence interval
The theoretical follow-up period estimation shall be the time interval between the date of inclusion and that on which the database is frozen.

The time-related parameters (PFS, OS) as well as the time to definitive deterioration of a quality of life score (scores) shall be estimated according to the Kaplan-Meier method and described with a median confidence interval (95%CI) and rates at defined periods.
Patients free from specific events at the end of the study (freezing of the study database) shall be censored, for the "Time" endpoint, at the date last seen.

Quality of life

A 5% deviations shall be defined as the minimum clinically significant difference/value.
Missing QoL data shall be analysed by calculating the rate of QLQ-C30 questionnaire completion during follow-up (observed/expected). The non-random inclusion of missing questionnaires shall also be calculated for this rate, based on the discontinuation of treatment and progression at each follow-up visit.
- The following shall be reported: The rate of patients showing an improvement in the QLQ-C30 score (any positive change and any change greater than 5 points), or stabilisation between the time of inclusion and the last follow-up, with respect to all eligible patients at inclusion and with respect to patients for whom the scores are available.
The time to definitive deterioration of the general health, physical function and fatigue scores.
- In order to study the progression over time of the quality of life scores, combined analysis of variance models for repeated measurements of each of the scores in each of the arms shall be applied.

F) TRIAL DURATION

INCLUSION PERIOD: **5 YEARS**
TREATMENT PERIOD: **UNTIL PROGRESSION**
MINIMUM FOLLOW-UP PERIOD: **2 YEARS**
OVERALL TRIAL DURATION: **7 YEARS**
IT IS STRONGLY RECOMMENDED THAT THE SITES PARTICIPATE TO THE TRANSLATIONAL RESEARCH (ANNEX 9)

** EudraCT Number will be requested after approval by the COS (Comité d'Orientation Stratégique)*

TABLE OF CONTENT

1. INTRODUCTION AND TRIAL RATIONALE

Colorectal cancer is one of the most widespread malignant diseases with an incidence of 148 / 100,000 in the United States [Jemal et al 2008] and of 90 / 100,000 in the European Union [Ferlay et al 2007]. Over the last 25 years, the median overall survival (OS) for stage IV metastatic colorectal cancer (CRC) has seen an improvement varying from 5 months to 2 years.

1.1. Role of Chemotherapy in Metastatic Colorectal Cancer

Since it was introduced onto the market, 5-fluorouracil (5-FU) has been the cornerstone in the treatment of metastatic colorectal cancer (mCRC). However, in recent years, the treatment of advanced stage CRC has seen major progress, particularly in deciding the choice of treatment based on biomarkers. Since 1996, six new active agents, including three cytotoxic agents (irinotecan, oxaliplatin and capecitabine) and three targeting agents (cetuximab, bevacizumab and panitumumab) have joined 5-fluorouracil.

The first early-phase clinical trials demonstrated that 5-FU associated with leucovorin (LV) improves the survival of patients presenting with mCRC compared to supportive care [Simmonds et al 2000]. Subsequently, the improvement in survival with irinotecan and oxaliplatin, approved for the first-line treatment of mCRC, along with associations such as FOLFIRI and FOLFOX, resulted in their extensive use.

A meta-analysis of 7 phase III trials evaluating therapeutic regimens associating 5-FU / leucovorin, oxaliplatin and irinotecan demonstrated that patients receiving the 3 drugs, regardless of the first doublet regimen used, exhibited prolonged survival compared to patients receiving a single doublet [Grothey et al 2004]. However, capecitabine per os exhibited equivalence to 5-FU and represents an well-tolerated alternative association for irinotecan or oxaliplatin.

After disease progression, a crossover second-line regimen associating fluoropyrimidine / oxaliplatin or fluoropyrimidine / irinotecan with another agent exhibited satisfactory response rates along with disease stabilised over a period of several months [Tournigand et al. 2004]. The FOLFIRI and FOLFOX6 associations were evaluated for post-progression crossover first-line or second-line treatment. Both arms exhibited similar response rates (first-line treatment: FOLFIRI 56% vs. FOLFOX 54% and second-line treatment FOLFIRI 4% vs. FOLFOX 15%). There were no significant differences in terms of progression-free survival (first-line treatment: FOLFIRI 8.5 months vs. FOLFOX 8.0 months and second-line treatment FOLFIRI 2.5 months vs. FOLFOX 4.2 months) or of overall survival (FOLFIRI-FOLFOX: 21.5 months vs. FOLFOX-FOLFIRI 20.6 months) (Table 1).

Table 1: *Objective tumour response after external review in Tournigand trial*

	1st-line treatment		2nd-line treatment	
	FOLFIRI (%)	**FOLFOX6 (%)**	**FOLFOX6 (%)**	**FOLFIRI (%)**
Overall response	56	54	15	4
Complete response	3	5	0	0
Partial response	53	49	15	4
Stable disease	23	27	48	30
Progression	14	13	19	51

The survival data in phase III trials such as OPTIMOX-2 have demonstrated that discontinuing treatment could have an adverse impact on progression-free survival (PFS) [Maindrault-Goebel et al 2007]. In this trial, the patients were randomised to receive a treatment of 6 cycles of FOLFOX7 followed by an interval without treatment, or a maintenance treatment with 5-FU/LV, followed by additional FOLFOX7 cycles after progression. The authors observed a trend towards an improvement in PFS in the patients having received 5-FU/LV during the treatment period, compared to those who had not received treatment (36 vs. 29 weeks; p=0.08).

Chemotherapy regimens associating standard cytotoxic agents with targeted treatment are the current gold-standard first- and second-line treatments for metastatic CRC.

1.2. Bevacizumab in Metastatic Colorectal Cancer

Progress in molecular biology has enabled better understanding of the cell signalling process involved in tumour growth and proliferation, subsequently enabling the development of target agents in the treatment of solid tumours. These agents have been devised to interfere with the major processes involved in tumour function. The most promising progress at the present time involves vascular endothelial growth factor (VEGF) inhibition. VEGF is a strong factor in tumour angiogenesis, permeability and tumour vascularisation survival [Gerber and Ferrara 2005]. VEGF inhibition induces the destruction of recent neo-microvascularisation and endothelial cell apoptosis. [Hicklin and Ellis 2005; Ferrara 2004; Erber et al 2004].

One of the most noteworthy VEGF pathway inhibitors is bevacizumab, a humanised monoclonal antibody targeting circulatory VEGF and preventing tumour angiogenesis. The binding of bevacizumab with VEGF prevents the latter from binding with its endothelial cell membrane receptors (Flt-1 and KDR). The interaction of VEGF with its receptors, in angiogenesis models, induces tumour growth and neovessel formation.

Trials have demonstrated the efficacy of associating bevacizumab with standard chemotherapy for patients suffering from wild-type and mutant KRAS, B-raf or p53 metastatic colorectal cancer [Hurwitz 2009, Ince 2005].

1.2.1. Preclinical trials with bevacizumab

In preclinical colorectal cancer models, anti-VEGF treatment exhibited inhibition of tumour growth compared to a control, as well as delayed effects due to neovessel growth and vascular base regrowth suppression [Inai et al 2004; Gerber and Ferrara 2005; Hicklin and Ellis 2005]. Further trials have demonstrated a reduction in the number and size of metastases, compared to controls [Melnyk et al 1999].

1.2.2. Clinical studies with bevacizumab

In one phase II study, 104 patients presenting with mCRC were randomised into 3 arms to receive either: 5-FU 500 mg/m² plus LV 500 mg/m² weekly, for 4 weeks, repeated every 6 weeks (Roswell Park regimen); or 5-FU/LV plus bevacizumab 10 mg/kg every 2 weeks (high-dose bevacizumab); or 5-FU/LV plus bevacizumab 5 mg/kg every 2 weeks (low-dose bevacizumab [Kabbinavar et al 2003]. The overall response rate was 17% for the 5-FU/LV arm, 40% for 5-FU/LV+ low-dose bevacizumab ($p<0.05$) and 24% for 5-FU/LV+ high-dose bevacizumab. The progression-free survival was 5.2 months for 5-FU/LV, 9.0 months for 5-FU/LV+ low-dose bevacizumab ($p<0.01$) and 7.2 months for 5-FU/LV+ high-dose bevacizumab. Following crossover, two patients out of 22 exhibited a partial response with bevacizumab alone. The adverse events included thrombocytopenia, the most significant adverse event with the death of one patient, as well as hypertension, proteinuria and transient epistaxis (duration < 5 minutes).

A second phase II study showed similar results, with bevacizumab plus 5-FU/LV compared to a placebo plus FU/LV as a first-line treatment for patients presenting with mCRC and not eligible for an irinotecan-based first-line treatment [Kabbinavar et al 2005]. The median survival was 16.6 months in the patients of the bevacizumab + 5-FU/LV group, and 12.9 months for those of the 5-FU/LV + placebo group ($p= 0.16$). The patients of the bevacizumab group exhibited a significantly prolonged median PFS (9.2 months), compared to that of the 5-FU/LV + placebo group (5.5 months; $p= 0.0002$). The more frequent grade 3 hypertension in the patients treated with bevacizumab (16% vs. 3% for the placebo) was, however, controllable.

1.2.3. bevacizumab in first-line treatment of mCRC: Phase III studies

Phase III trials have demonstrated the efficacy and tolerance of bevacizumab associated with treatments with 5-FU. The first study (AVF2107g) included 815 chemonaive patients presenting with mCRC: the efficacy of the IFL regimen (irinotecan 125 mg/m², in 90-minute infusion, followed by LV 20 mg/m² by IV bolus, followed by 5-FU 500 mg/m² by IV bolus (once/week for 4 week, cycle repeated every 6 weeks) was compared to that of IFL plus bevacizumab (5 mg/kg IV every 2 weeks [Hurwitz et al 2004]. Adding bevacizumab prolonged the overall survival (20.3 vs. 15.6 months for IFL + placebo) and the PFS (10.6 vs. 6.2 months for IFL + placebo) significantly, whereas the response rate and the response time were significantly greater (10.4 months vs. 7.1 months for IFL + placebo; $p=0.0014$) in the patients of the bevacizumab group (see Figure 1). The grade 3 arterial hypertension reported in 11% of the patients of the bevacizumab group and 2% of the IFL group ($p<0.01$) was controllable. Thrombotic events affected 19% of the patients of the bevacizumab plus IFL group and 16% of the IFL group. In the light of these results, in 2004, the FDA approved the association of the 5-FU plus bevacizumab chemotherapy regimen in the first-line treatment of patients presenting with mCRC.

The second study relating to the bevacizumab/5-FU/LV association demonstrated similar efficacy and tolerance to that of IFL [Hurwitz et al 2005]. Patients presenting with mCRC were randomised to receive: either IFL plus placebo; or IFL plus bevacizumab 5 mg, or bevacizumab 5 mg plus 5-FU/LV (5-FU 500 mg/m² plus LV 500 mg/m² (once/week for 4 weeks, cycle repeated every 6 weeks) (Roswell Park regimen). After an intermediate analysis conforming the tolerance in the bevacizumab + IFL arm, inclusion in the bevacizumab plus 5-FU/LV arm was discontinued. Similar response and survival rates were observed in both groups (40.0% vs. 37% for IFL + placebo) and (18.3 vs. 15.1 months for IFL + placebo) respectively. The toxicities were those expected for 5-FU/LV and IFL, with a slight increase in hypertension in the bevacizumab arm (grade 3 AHT, 18% and 3% for bevacizumab + 5-FU/LV and IFL, respectively) and bleeding (grade 1/2 epistaxis for 32% and 10%, respectively). This study demonstrated that associating bevacizumab and 5-FU/LV is an attractive first-line treatment for patients presenting with mCRC.

Further statistical analyses were conducted to assess the KRAS expression of the tumour tissues of the AVF 2107 trial in order to describe the clinical benefit in patients having mCRC with a KRAS mutation and treated with bevacizumab [Hurwitz 2009]. The median PFS was prolonged significantly in wild-type KRAS patients treated with bevacizumab (13.5 versus 7.4 months; hazard ratio 0.44, $p < 0.0001$) and mutant KRAS patients (9.3 versus 5.5 months; hazard ratio 0.41, $p<0.0008$). A significantly higher response rate in the IFL plus bevacizumab group was observed in the patients exhibiting wild-type KRAS expression (60.0% versus 37.3%, $p<0.006$), compared to the mutant KRAS group (43.2% versus 41.2%). The authors concluded that bevacizumab offered a clinically significant benefit for patients with mCRC equally well with wild-type and mutant KRAS expression.

The results of the large-scale study XELOX-1/NO 16966 demonstrated that bevacizumab could also be associated with oxaliplatin-based treatments [Saltz et al. 2008]. Associating bevacizumab with the IFL therapeutic regimen improved the overall survival and progress-free survival significantly, and enabled the amendment of the study to evaluate the potential effect of adding bevacizumab to XELOX or FOLFOX-4. The resulting study became a placebo-controlled, 2x2 study, the patients were randomised to receive either bevacizumab, or the placebo associated with XELOX or FOLFOX-4. The addition of bevacizumab to oxaliplatin-based chemotherapy improved the PFS significantly, compared to chemotherapy alone. The patients receiving bevacizumab exhibited a PFS of 9.4 months, whereas that of the placebo group was 8.0 months (HR: 0.83 [95% CI: 0.72-0.95]; p=0.0023) (see Figure 1 paragraph 1.3). The rate of treatment discontinuation related to adverse events was higher in the patients of the bevacizumab group (30% vs. 21% for the placebo), these discontinuations being for the most part due to chemotherapy rather than bevacizumab. The incidence of adverse events due specifically to bevacizumab was low. Grade 3/4 hypertension was 4% in the bevacizumab group, and 1% for the placebo group; grade 3/4 bleeding and thrombotic events were 2% each in the bevacizumab group, and 1% in the placebo group.

In the light of the trials mentioned above, the first-line treatment strategy for patients with mCRC involves associating bevacizumab with a fluoropyrimidine/oxaliplatin or irinotecan chemotherapy regimen.

1.2.4. Bevacizumab in second-line treatment of mCRC: Phase III studies

The efficacy and tolerance of bevacizumab were also evaluated for the second-line treatment of mCRC. Patients having experienced therapeutic failure with irinotecan and 5-FU were randomised into one of the following three arms: FOLFOX4 + bevacizumab (n=286), FOLFOX4 (n=291), or bevacizumab alone (n=243) [Giantonio et al. 2007]. Associating bevacizumab with FOLFOX-4 chemotherapy improved the overall survival significantly: the

median OS of the patients of the FOLFOX4 + bevacizumab group was 12.9 months vs. 10.8 months for the FOLFOX4 group (HR 0.75; p=0.0011) (Table 2). The median OS of the patients of the bevacizumab alone group was 10.2 months. The PFS was prolonged significantly with bevacizumab (7.3 vs. 4.7 months for bevacizumab + FOLFOX4 vs. FOLFOX4, respectively; HR 0.61; p<0.0001). Furthermore, the treatment response was greater in the patients of the bevacizumab + FOLFOX4 group, compared to the FOLFOX4 group (22.7% vs. 8.6%; p<0.0001).

Table 2: *Efficacy of bevacizumab + FOLFOX4, FOLFOX4 alone, or bevacizumab alone as second-line treatment*

	Bevacizumab + FOLFOX4 (n=287)	**FOLFOX4 (n=285)**	**Bevacizumab (n=234)**
Median OS, months	12.9**	10.8	10.2
Median PFS, months	7.3***	4.7	2.7
ORR, %	22.7***	8.6	3.3
Complete response	1.7	0.7	0
Partial response	21.0	7.9	3.3

ORR: objective response rate; OS: overall survival; PFS: progression-free survival
**p<0.01 *vs.* FOLFOX4; ***p<0.001 *vs.* FOLFOX4

The grade 3/4 adverse events are summarised in table 3. The incidence of adverse events giving rise to discontinuation of the treatment, or of mortality at 60 days regardless of the cause, was not significantly different between the 3 groups.

Table 3: *Adverse events associated with bevacizumab + FOLFOX4, FOLFOX4 alone, or bevacizumab alone as second-line treatment*

	Bevacizumab + FOLFOX4 (n=287)	**FOLFOX4 (n=285)**	**Bevacizumab (n=234)**
Hypertension	6.2**	1.8	7.3
Bleeding	3.4*	0.4	2.1
Vomiting	10.1**	3.2	4.7

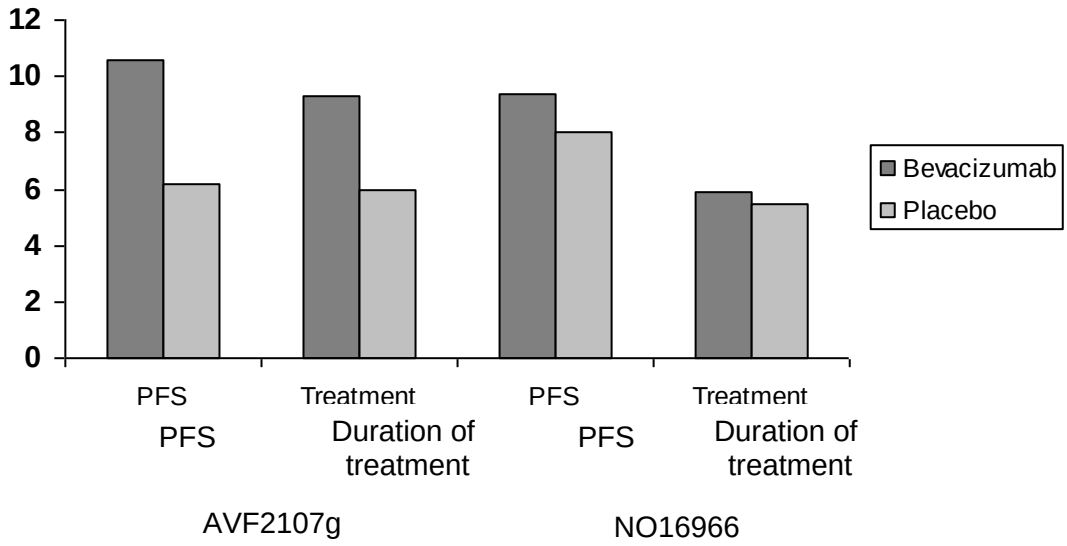
On the basis of the results of these trials, bevacizumab, in association with a fluoropyrimidine chemotherapy regimen, is currently recommended as a second-line treatment for patients presenting with mCRC, and never having previously received this agent as a first-line treatment. However, due to the lack of data available, the guidelines stipulate that it is not recommended to continue bevacizumab as a second-line treatment following a first progression after a bevacizumab-based regimen (NCCN 2009).

1.3. Treatment Duration with Bevacizumab: Optimising Results in mCRC

Preclinical studies have demonstrated that VEGF antibody was expressed during all tumour growth phases. They have also demonstrated that anti-VEGF agents have an effect on angiogenesis and that their suppression induced tumour revascularisation [Mancuso et al 2006]. Tumour regression was achieved and maintained within the framework of continuous

VEGF inhibition [Klement et al 2000; Klement et al 2002]. These observations raise the question of whether to continue mCRC treatment with bevacizumab after progression.
In the study AVF2107g, the prolonged treatment duration of the bevacizumab arm resulted in a significant improvement in PFS, compared to that of the placebo (Figure 1). In the XELOX-1/NO trial, the treatment duration was similar for the placebo and bevacizumab arms (approximately 6 months). Adding bevacizumab resulted in a superior PFS to that of the placebo, but to a lesser degree than in the study AVF2107g, apparently due to the discontinuation of treatment.

Figure 1: *Duration of treatment and progression-free survival in comparative phase III studies on bevacizumab / placebo* [Hurwitz et al 2004; Saltz et al 2008]



A crossover comparative study of the "general" and "treatment-related" PFS rates for the AVF2107g trial demonstrated a similar progression-free survival. The same analyses showed a considerable difference with XELOX-1/NO16966. The "general" PFS analysis showed a lower Hazard-Ratio for AVF2107g compared to XELOX-1/NO16966 (HR=0.58 vs. 0.83, respectively). These results were in contrast with the "treatment-related" analysis which did not demonstrate any difference between the two trials (HR=0.54 vs. 0.63). The majority of AVF2107g patients having been treated until progression, this comparison reflects the superiority of the efficacy of bevacizumab administered until disease progression.

Major data relating to continuing treatment with bevacizumab after disease progression can be sourced in BRiTE, a trial including 1953 patients suitable for evaluation with mCRC and having received bevacizumab as a first-line treatment [Grothey et al 2008]. A total of 1445 patients exhibited disease progression (74%), 642 patients (44%) received post-progression treatment with bevacizumab, 531 patients (37%) received a treatment other than bevacizumab, and 253 patients (18%), no treatment. Table 4 demonstrates the superiority of the overall survival and of the median overall survival after a first progression in patients who continued the treatment with bevacizumab compared to those who had never taken bevacizumab after a first progression. In a multivariate analysis, the post-progression use of bevacizumab was associated with a significant reduction in the risk of death (HR, 0.48; p<0.001), whereas no post-progression treatment was associated with a significant increase in the risk of death (HR, 2.01; p<0.001), compared with a treatment without bevacizumab after disease progression.

Table 4: *Survival data for patients presenting with progression: BRiTE study*

	Post-progression treatment

Data item	Total number of patients	With Bevacizumab	Without Bevacizumab	No treatment
Number of deaths, n (%)	932 (48)	260 (41)	306 (58)	168 (66)
Median OS, months	25.1	31.8	19.9	12.6
(95% CI)	(23.4-27.5)	(27.9-NE)	(18.0-22.0)	(10.6-15.7)
1-year survival, %	74.7	87.7	77.3	52.5
(95% CI)	(72.7-76.7)	(85.2-90.3)	(73.7-80.9)	(46.2-58.8)
Median OS post-PD, months	12.0	19.2	9.5	3.6
(95% CI)	(11.1-13.3)	(16.8-20.7)	(8.4-11.2)	(2.7-4.3)
CI: confidence interval; NE: not estimated; OS: overall survival; PD: progressive disease				

In this study, the tolerance of bevacizumab was acceptable. There was no increase in adverse events compared to bevacizumab monotherapy prior to disease progression. The post-progression risk of hypertension (bevacizumab group, 24.6% vs. 19.2% non-bevacizumab group respectively), thrombotic arterial events (0.9 vs. 0.2%), bleeding (0.9 vs. 0.2%), and gastrointestinal perforation (0.6 vs. 0.4%) was very low.

1.4. Cetuximab in metastatic colorectal cancer

The epithelial growth factor receptor (EGFR) is a transmembrane receptor with tyrosine kinase activity. After binding with the ligand, two major signalling pathways are activated. These pathways include the RAS-RAF-MAPK pathway essentially involved in cell proliferation and the PI3K-PTEN-AKT pathway, which is more particularly involved in cell motility and survival [Baselga 2001]. These EGF receptor signalling pathways are deregulated in 75% to 89% of colorectal cancers [Saltz 2004]. Cetuximab, a monoclonal antibody, specifically inhibits EGF receptor. Binding of cetuximab also stimulates receptor internalisation and degradation [Hadari 2004] and may also induce an antibody-dependent cell-mediated cytotoxicity reaction [Zhang 2007].

1.4.1. Cetuximab and KRAS and *BRAF* mutations

Cetuximab was approved in Europe in 2004 in irinotecan-refractory metastatic colorectal cancer, expressing EGFR, [Cunningham et al 2004]. However, it soon became clear that patients not expressing EGFR did not benefit from the treatment to the same extent as EGFR-positive patients [Chung 2005]. Cetuximab has demonstrated its efficacy with a clinical benefit in 10 to 20% of patients [Meyerhardt 2005]. Factors other than EGFR could be predictive markers exhibiting superior (or low) efficacy for this target agent or other related substances. KRAS, a small G protein, an essential component downstream of the EGFR cascade signalling pathway, may acquire active exon 2 mutations, thereby inhibiting the effects of the EGFR pathway, [Baselga, 2001] and neutralising EGFR inhibitors [Karapetis 2008]. Consequently, EGFR signalling only controls wild-type KRAS [Karapetis 2008, Amado 2008]. Furthermore, as the incidence of KRAS mutations only applies to 30% to 40% of non-responder patients [Di Nicolantonio 2008], the identification of other genetic determinants of primary resistance to targeted EGFR treatments in colorectal cancer is crucial.
Recent discoveries resulting from a retrospective study appear to suggest that the presence of wild-type B-raf (a serine-threonine kinase, mutant in approximately 10% of mCRC) is required for response to cetuximab [Di Nicolantonio 2008]. The *BRAF* V600E mutation was detected in

11 patients out of 79 exhibiting wild-type KRAS. None of the mutant BRAF patients responded to the treatment, whereas none of the responder patients exhibited a BRAF mutation (p=0.029). The mutant BRAF patients, compared to the wild-type patients, exhibited significantly progression-free survival (p=0.011) and OS (p<0.0001). A further study involving 586 patients demonstrated that KRAS, B-raf kinase (BRAF) or phosphatidylinositol 3-kinase (PI3K) type gene mutations were also associated with significantly lower progression-free survival [Barault et al 2008].

1.4.2. Clinical studies with cetuximab

A number of non-randomised studies have demonstrated little or no benefit in patients presenting with mutant KRAS, treated with anti-EGFR agents as monotherapy or in association with chemotherapy (Table 5). Randomised studies subsequently confirmed these results.

Table 5: *Results of single-arm cetuximab studies analysing the correlation between efficacy and KRAS status in CRC.*

Studies	Treatment	Total number of patients	Response Rate (%)	
			Mutant KRAS	Wild-type KRAS
Benvenuti 2007	P or C or C ± CT	48	6	31
De Roock 2008	C ± CT	113	0	40
Finocchiaro 2007	C ± CT	81	6	26
Di Fiore 2007	C ± CT	59	0	28
Khambata 2007	C	80	0	10
Liévre 2008	C ± CT	89	0	40

C: cetuximab; P: panitumumab; CT: chemotherapy

In OPUS, a phase II evaluating FOLFOX (fluorouracil + leucovorin + oxaliplatin, by IV bolus and infusion) and cetuximab as first-line treatment, the wild-type KRAS patients displayed a benefit with cetuximab plus FOLFOX, compared to the patients receiving FOLFOX alone, both in terms of response rate (61% vs. 37%; p<0.01) and of PFS (7.7 v 7.2 months; p<0.02) [Bokemeyer 2008]. However, the patients exhibiting mutant KRAS and receiving FOLFOX plus cetuximab displayed a markedly lower PFS (5.2 vs. 8.6 months; p<0.02) than those receiving FOLFOX alone, and a reasonably lower response rate (33% vs. 49%; p<0.1).

In EVEREST, a phase I/II study evaluating, in terms of response rate, the relationship between skin reaction and the progressive increase in the dose of cetuximab associated with irinotecan. The predictive value of KRAS was also tested in the evaluation of the skin reaction supposed to substitute the pharmacokinetics or pharmacodynamics. The wild-type KRAS patients did not display any difference and the response rates were 30% to 42%, respectively, in the low-dose and high-dose arms; a 0% response rate was observed in mutant KRAS patients [Jimeno et al 2008].

In BOND, a phase II study on the second-line treatment of MCRC, associating two monoclonal antibodies: bevacizumab and cetuximab. According to a previous randomised trial, an improvement in the response rate (22.9% vs. 10.8%) and in the median time to progression

(4.1 months vs 1.5 months) was observed in the treatment group associating both antibodies compared to monotherapy. The results of the BOND trials suggest a benefit for the EGFR – angiogenic inhibitor association. The time to progression (TTP) of the BOND-2 study is greater in the cetuximab plus bevacizumab group (5.6 months) and the cetuximab/bevacizumab/irinotecan group (7.9 months) compared to the cetuximab plus irinotecan group (4.1 months) in the BOND-1 study. The overall survival was 8.6 months in the BOND-1 trial, compared to 10.2 months and 18.0 months, respectively, for BOND-2 [Cunningham et al 2004; Saltz 2007].

MABEL – "Monoclonal Antibody Cetuximab in a European Pre-License", an international phase II trial, confirmed the results of the BOND trials [Wilke 2008]. The primary objective was to evaluate the progression-free survival at 12 weeks for second-line treatment. The initial dose of cetuximab of 400 mg/m² was followed by 250 mg/m² weekly. Irinotecan, at a weekly dose of 125 mg/m² (according to the previous treatment), was administered every 2 weeks for 4 to 6 weeks, or at a dose of 180 mg/m² every 2 weeks and every 3 weeks at 350 mg/m². The intention-to-treat population for the tolerance analysis was 1147 patients divided into irinotecan weekly (n = 93), every 2 weeks (n = 670), every 3 weeks (n = 356), or at another dose (n = 28). The PFS rate at 12 weeks was 61% and the median survival 9.2 months (Table 6).

Table 6: *Efficacy results: Mabel trial*

Efficacy parameters	C + irinotecan 125 mg/m² 1 x week (n=93)	C + irinotecan 180 mg/m² every 2 weeks (n=670)	C + irinotecan 350 mg/m² every 3 weeks (n=356)	C + other irinotecan dose (n=28)	Total number of patients (N=1147)
Median PFS (months)	3.0	3.2	4.6	2.7	3.2
Median OS (months)	8.3	9.2	10.3	7.0	9.2
Response rate (%)	17	116	92	6	231
Disease control rate (%)	40	275	191	13	519

This study also demonstrated the satisfactory tolerance of the cetuximab plus irinotecan association, the treatment-related and most frequently reported grade 3/4 adverse events were typical for irinotecan, diarrhoea (19%), neutropenia (10%) and asthenia (6%) and for cetuximab, skin irritation (7%), and adverse events associating acne-skin irritation (13.3%). The rate of infusion-related and grade 3 to 4 reactions was 1% in the patients receiving an antihistamine in conjunction with corticosteroid-based premedication, and was lower than that reported in previous studies. The degrees of toxicity were similar to those reported for the treatment association arm for the BOND study, and cetuximab did not appear to increase the incidence or severity of the adverse events (AE) associated with irinotecan, or vice-versa.

1.4.3. Phase III studies with Cetuximab: First-line treatment of mCRC

In CRYSTAL, a phase III trial, patients presenting with mCRC expressing EGFR were randomised to receive either FOLFIRI as a first-line treatment (fluorouracil + leucovorin + irinotecan, by bolus and perfusion) (n=599) or FOLFIRI plus bevacizumab (n=599) [Van Cutsem 2008]. The results, in terms of benefit for PFS or in terms of overall response rates, were not significant. FOLFIRI plus cetuximab exhibited a median PFS of 8.9 months versus 8 months (hazard ratio (HR) of 0.851; p = 0.0479), the overall response rate was 46.9% with FOLFIRI plus cetuximab compared to 38.7% for FOLFIRI (p = 0.0038). However, the later separation of the PFS curves clearly shows that a subgroup of patients benefited from adding cetuximab.
A retrospective study conducted on a patient subgroup of the intention-to-treat population suitable for analysis for KRAS status demonstrated that the benefit of cetuximab appears to be restricted to patients not having KRAS mutations [Jimeno et al 2008].

1.4.4. Phase III studies with Cetuximab: Second-line treatment of mCRC

A phase III conducted jointly by the "National Cancer Institute of Canada Clinical Trials Group" (NCIC CTG) and AGITG "Australasian Gastro-Intestinal Trials Group" demonstrated that, in patients presenting with mCRC and subject to chemotherapy failure, subsequently benefiting from cetuximab monotherapy, exhibited an improvement in overall survival, progression-free survival, and a superior quality of life than best supportive/palliative care/management alone [Jonker 2007]. However, cetuximab resistance was frequent: the first evaluation of the response showed disease progression in over 50% of the patients treated. A correlation analysis was conducted to determine the impact of KRAS gene mutation, during this trial, on the effect of cetuximab in terms of survival. Treating with cetuximab practically doubled the median survival and PFS in patients presenting with wild-type KRAS tumours, compared to

palliative care alone. The benefit of survival was not significant with cetuximab, only in patients carrying KRAS mutations [Karapetis et al 2008].
The phase III, open-label, multi-centre study, EPIC (Cetuximab Plus Irinotecan in Metastatic Colorectal Cancer) related to 1298 patients presenting with mCRC expressing epithelial growth factor receptor. These patients had experienced therapeutic failure after a first-line treatment with fluoropyrimidine and oxaliplatin. The patients received cetuximab (400 mg/m² day 1 followed by 250 mg/m² weekly) plus irinotecan (350 mg/m² every 3 weeks) or irinotecan alone [Sobrero et al 2008]. The data from EPIC show a significant improvement in the PFS and response rate with cetuximab plus irinotecan. However, the primary objective of overall survival and of the superiority of cetuximab plus irinotecan compared to irinotecan alone did not show statistically significant differences. The secondary objectives of progression-free survival, response rate and quality of life nonetheless favoured the cetuximab/irinotecan arm. The tolerance profile of cetuximab plus irinotecan was predictable, controllable and consistent with previous studies. The toxicity of cetuximab plus irinotecan did not increase significantly, except for acneiform eruption, diarrhoea and hydroelectrolytic balance impairment.

Recently, a number of phase III studies demonstrated the lack of benefit of an anti-EGFR treatment associated with FOLFOX or with FOLRIRI in patients having CRC presenting with a rare KRAS gene (exons 3 and 4) and NRAS gene mutation representing approximately 10% of additional patients for whom this treatment is not recommended [Douillard JY et al. NEJM 2013, Stintzing S. ESMO 2013]

On the basis of the results of the studies mentioned above, the EGFR inhibitor cetuximab is approved in the second-line treatment of metastatic colorectal cancer.
The purpose of this phase II randomised study is to evaluate the efficacy of Cetuximab versus Bevacizumab in patients suffering from wild-type RAS (KRAS and NRAS) metastatic colorectal cancer subject to progression after a first-line chemotherapy regimen based on fluoropyrimidine associated with bevacizumab.

1.5. Study justification

Targeted therapy has helped improve survival in metastatic colorectal cancer. Bevacizumab, an anti-VEGF agent, has demonstrated its efficacy in association with first- and second-line chemotherapy in patients with mCRC. In a second-line treatment, adding bevacizumab to a FOLFOX-4 chemotherapy regimen has helped improve overall survival in patients having received a first-line chemotherapy regimen based on fluoropyrimidines and irinotecan and not having received bevacizumab or oxaliplatin previously. Cetuximab, an anti-EGFR agent, for its part, has demonstrated its efficacy in association with irinotecan as a second-line treatment for patients with mCRC.
The association of these two monoclonal antibodies appears to be beneficial according to the associated chemotherapy. In the BOND2 study, associating bevacizumab with irinotecan offers a superior benefit compared to associating bevacizumab with cetuximab. However, associating cetuximab and bevacizumab with capecitabine and oxaliplatin lowers the progression-free survival and impairs quality of life in patients with untreated mCRC [Tol et al 2009].
No study has compared the efficacy and tolerance of bevacizumab compared to cetuximab as a second-line treatment after a first-line treatment based on bevacizumab. The benefit of this study lies in the comparison of the efficacy/tolerance ratio of cetuximab and bevacizumab. For each targeted therapy, we hope to find an efficacy/tolerance ratio suitable for evaluating the benefit of each in the therapeutic strategy of mCRC.

2. TRIAL OBJECTIVES

2.1 Primary objective

Evaluate the progress-free survival (PFS) at 4 months.

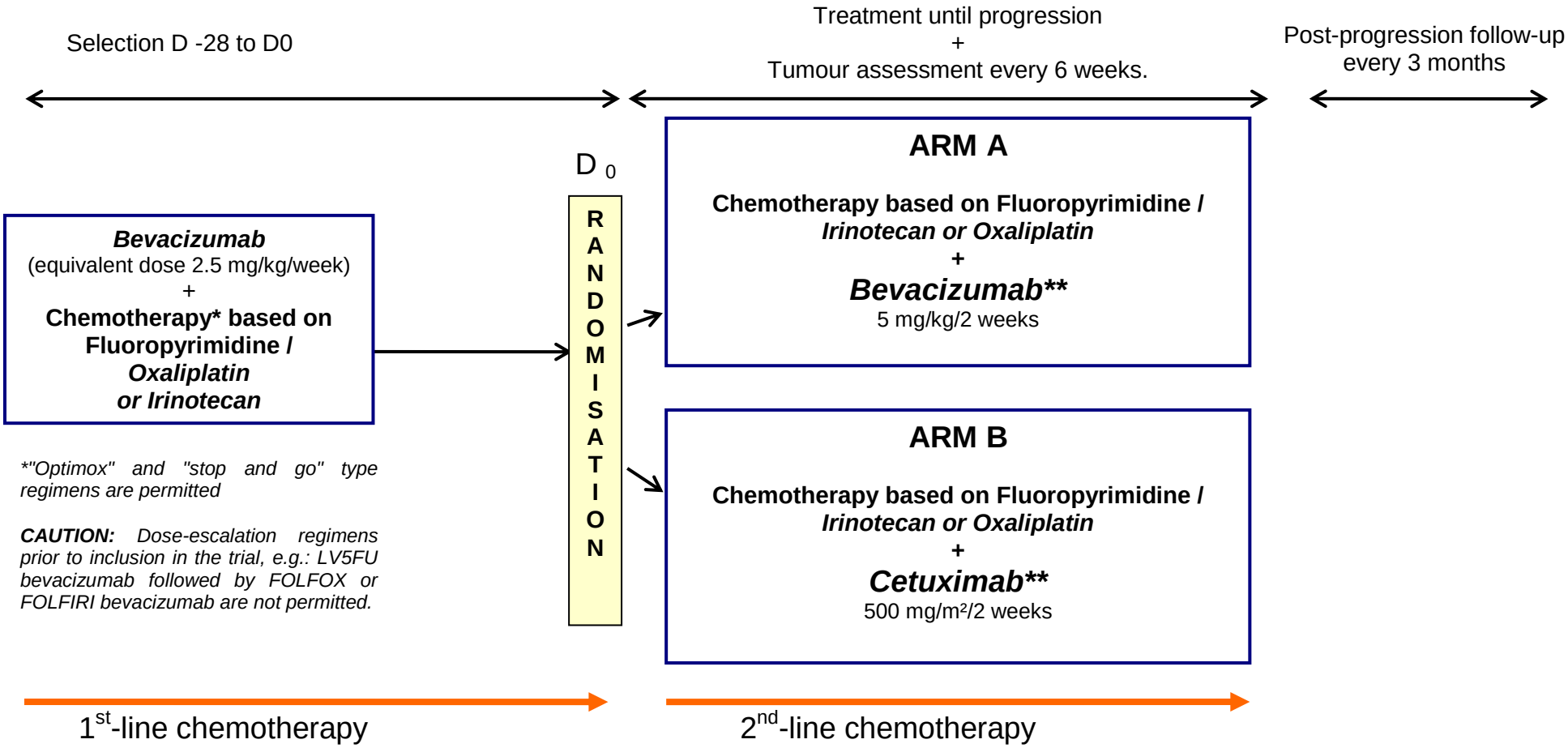
2.2 Secondary objectives

- Evaluate the objective response rate (OR) (= complete responses CR and partial responses PR) as per RECIST v1.1 criteria (appendix No. 3)
- Evaluate the progression-free survival (PFS)
- Evaluate the overall survival (OS)
- Evaluate the overall survival from the date of the 1st-line chemotherapy of the metastatic disease.
- Evaluate the treatment tolerance (NCI CTC AE V4 criteria (appendix 5), except peripheral neurological toxicity (Levi scale, appendix 4)
- Evaluate the Quality of Life as per EORTC QLQ-C30 criteria (appendix 7 and 8)

- Study the potential predictive factors for the response to anti-EGFR and anti-VEGF treatments (appendix No. 9)

3. METHODOLOGY

Randomised, multicentre, open-label, phase II trial, evaluating the progression-free survival at 4 months of fluoropyrimidine-based standard chemotherapy associated with either cetuximab or bevacizumab, in wild-type RAS (KRAS and NRAS) metastatic colorectal cancer patients with progressive disease after receiving first-line treatment with bevacizumab.



*"Optimox" and "stop and go" type regimens are permitted

CAUTION: *Dose-escalation regimens prior to inclusion in the trial, e.g.: LV5FU bevacizumab followed by FOLFOX or FOLFIRI bevacizumab are not permitted.*

** In the event of definitive discontinuation of chemotherapy for toxicity reasons, bevacizumab or cetuximab shall be administered until disease progression, except in the event of unacceptable toxicity induced by the targeted therapy, or following a decision by the patient or the investigator.

4. PATIENT SELECTION

4.1 Inclusion criteria

1. Histologically or cytologically proven colorectal adenocarcinoma expressing wild-type RAS (KRAS and NRAS).
2. Progressive metastatic disease after first-line treatment with only one previous chemotherapy based on 5-FU (IV or per os) with irinotecan or oxaliplatin associated with bevacizumab.
3. Prior fluoropyrimidine-based adjuvant chemotherapy (for the primary tumor) with oxaliplatin is allowed if the time interval between the end of this chemotherapy and the beginning of the first-line metastatic treatment is ≥6 months.
4. Measurable disease (at least one measurable metastatic lesion by RECIST V1.1 criteria, with lesion not located in a previous field of radiation).
5. Previous radiotherapy is authorized if discontinued ≥15 days prior to randomization and if the measurable metastatic lesions are outside the radiation area.
6. Sites of disease evaluated within 28 days prior to randomization with thoracic-abdominal-pelvic CT scan (or abdominal-pelvic MRI and chest X-ray)
7. Age ≥18 years
8. Patient with ECOG 0 or 1
9. Life expectancy ≥12 weeks
10. Hematologic function: polynuclear neutrophils ≥ $1.5.10^9$/L; platelets ≥100.10^9/L; haemoglobin ≥9 g/dL
11. Hepatic function: transaminases ≤2.5 times upper limit of normal (ULN) (≤5 ULN in case of hepatic metastases), alkaline phosphatases ≤2.5 x ULN (≤5 ULN in case of hepatic metastases), total bilirubin ≤1.5 x ULN
12. Renal function: creatinemia ≤1.5 x ULN; creatinine clearance ≥50 mL/min (Cockcroft and Gault); urine test strip <+2. If proteinuria is ≥+2 at inclusion, the serum urea test must be redone and show proteinuria ≤1 g/L within 24 h)
13. Patients having completed the EORTC QLQ-C30 quality of life form
14. Negative pregnancy test for women of child-bearing age
15. Information given to the patient and signed informed consent
16. Public Health insurance coverage

*schemes like « optimox » or « stop and go » are allowed.

4.2 Non inclusion criteria

1) Known meningeal or brain metastases
2) Patient previously treated with an anti-EGFR
3) Specific contraindication or known hypersensitivity to one of the study treatments
4) Patients who received a dose de-escalation scheme e.g.LV5FU bevacizumab followed by FOLFOX or FOLFIRI with bevacizumab.
5) Patient with known allergy or hypersensitivity to monoclonal antibodies (bevacizumab, cetuximab), or to Chinese hamster ovarian cell products or any other humanized or recombined antibodies or any other chemotherapies under study, and their excipients.
6) Clinically significant coronaries affection or myocardial infarction within 6 months prior to inclusion.
7) Peripheral neuropathy of grade >1 (CTCAE scale version 4.0).

8) Known dihydropyrimidine dehydrogenase (DPD) deficiency.
9) Acute intestinal obstruction or sub-obstruction, history of inflammatory intestinal disease or extended resection of the small intestine. Presence of a colic prosthesis.
10) Unhealed wound, active gastric or duodenal ulcer, or bone fracture
11) History of abdominal fistulas, trachea-oesophageal fistulas or any other grade 4, gastro-intestinal perforations or non-gastrointestinal fistulas or intra-abdominal abscesses during the 6 months before inclusion.
12) Uncontrolled arterial hypertension (systolic pressure >150 mmHg and/or diastolic pressure >100 mmHg with and without antihypertensive medication. Patients with high hypertension are eligible if antihypertensive medication lowers their arterial pressure to the level specified by the inclusion criterion.
13) History of hypertensive crisis or hypertensive encephalopathy
14) Thromboembolic event in the 6 months before inclusion (e.g. transitory ischemic stroke, stroke, subarachnoid haemorrhage) except peripheral deep vein thrombosis treated with anticoagulants
15) Other concomitant malignancy or history of cancer (except in situ carcinoma of the cervix, or non-melanoma skin cancer, treated with curative intent treatment) except if considered in complete remission for at least 5 years before randomization.
16) Existence of any other pathology, metabolic problem, anomaly during the clinical examination or biological anomaly which may reasonable suspect an underlying pathology which would contra-indicate the use of the study medication or any other risk of complication related to the treatment.
17) Any treatment including an experimental drug, or participation in another clinical trial within 28 days before randomisation.
18) Pregnant women, or women who could possibly be pregnant (or who expect to fall pregnant within 6 months of the end of treatment), or who are breast feeding are not eligible.
19) Men and women of child-bearing age who do not accept to use a highly effective contraceptive (as per currently acceptable institutional standards) or abstinence during the study and for the 6 months after the last administration of the study treatments.
20) Persons deprived of liberty or under guardianship.
21) Psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule.

5. PATIENT RANDOMISATION

After the patient information document and consent form have been signed and the results of the initial inclusion assessment have been validated, eligible patients may be randomised.

On the day of randomisation, the investigator should ensure that the assessments required for inclusion and the questionnaire QLQ-C30 have been processed and completed in the allotted time-frame. (See section 7)

Randomisation shall be carried out by the investigator using TenAlea software, by logging onto the following address**:** **https://fr.tenalea.net/leclerc//.**

Once the randomisation has been completed by the investigator registered in the study, the investigator shall receive email confirmation in pdf format. This confirmation shall also be sent to the Biostatistics and Epidemiology Department at Centre Georges-François Leclerc and to R&D UNICANCER.

For web-based randomisation, the investigator should enter his/her login and password provided immediately after the set-up visit at the centre.

In the event of a problem during randomisation, or if unable to log onto the website, contact the Biostatistics and Epidemiology department at Centre Georges-François Leclerc by phone or by fax to carry out the randomisation.

Biostatistics and Epidemiology Unit at Centre Georges-François Leclerc Monday to Friday from 9 a.m. to 6 p.m. Reception phone: +33 (0)3.80.73. 77.89 **Fax: +33 (0)3.80.73.77.65**

Randomisation shall be carried out by minimisation and stratified on:

- 1st-line chemotherapy: chemotherapy based on fluoropyrimidine/oxaliplatin versus fluoropyrimidine/irinotecan
- Progression-free survival of the 1st-line treatment ≤ 9 months versus > 9 months
- The centre

The treatment must commence within 7 days following randomisation.

6. TREATMENTS

6.1 Description of study treatments

Patients having signed their consent form and complying with all inclusion and non-inclusion criteria shall be randomised into either:

arm A = **bevacizumab** + fluoropyrimidine-based standard chemotherapy
arm B = **cetuximab** + fluoropyrimidine-based standard chemotherapy

The study products (SP) are **bevacizumab** and **cetuximab.**
The associated treatments are oxaliplatin, 5-Fu and irinotecan

Bevacizumab shall be supplied free of charge by the sponsor assisted by Roche Laboratories. The other medicinal products shall be provided by the investigation centre.

The treatment duration in this study is envisaged until disease progression or unacceptable toxicity.

The choice of post-progression treatment shall be left up to the investigator. Patients whose disease progression has been documented shall cease to receive the study treatment and shall be the subject of follow-up until the time of their death.

6.1.1 Bevacizumab

Bevacizumab must be prepared by a health professional in compliance with asepsis-related precautions. Take up the volume of bevacizumab required to prepare a dose. Discard any unused fraction remaining in the vial, as the product does not contain preservative. Medicinal products

intended for parenteral administration must be examined visually to detect any particles or colour anomalies prior to their administration.

No incompatibility between bevacizumab and the bags, or the polyvinyl chloride or polyolefin infusion devices has been observed.

When bevacizumab has been mixed with a bag of sterile saline solution, the solution must be administered within 8 hours. Bevacizumab must not be administered or mixed with glucose solutions (see Summary of Product Characteristics).

A mechanism regulating the infusion rate shall be used for all infusions. When the bag is empty, a 50 ml volume of 0.9% saline shall be added or another bag shall be added and infusion shall be continued for a volume equal to that of the tube to ensure that bevacizumab is administered in full. The saline solution subsequently injected to drain the tube shall not affect the study treatment infusion time.

Chemical and physical stability during use has been demonstrated over a period of 48 hours between 2°C and 30°C in a 9 mg/ml (0.9%) sodium chloride solution for injection. From a microbiological viewpoint, immediate use is recommended. If the product is not used immediately after reconstitution, the shelf-life and storage conditions fall under the user's responsibility and normally should not exceed 24 hours in a refrigerator between 2°C and 8°C, unless the dilution has been carried out under controlled aseptic conditions.

Do not freeze. Store the vial in its outer packaging, protected from light. Do not administer via direct IV or bolus. In the event of extravasation of the study treatment, the following procedure shall be followed:

- Discontinue infusion
- If the residual product volume is significant, resume infusion on another site on the same arm.

The doses of bevacizumab shall be calculated for each patient in milligrams per kilogram (mg/kg). The patient's weight recorded during the inclusion visit shall be the reference weight throughout the study (patients shall receive the same dose throughout the study). However, if, during the treatment period. a patient exhibits a change of over 10% from his/her weight at inclusion, the doses of bevacizumab shall be recalculated. Bevacizumab shall be administered for a maximum weight of 135 kg.

6.1.2 Cetuximab

The dosage selected in the protocol is different to that mentioned in the SPC, i.e. 500 mg/m² administered by IV infusion **every 14 days,** until disease progression or unacceptable toxicity.

When administering Cetuximab, the tube must be equipped with a built-in 0.22 micron low protein fixation filter. Do not administer cetuximab by IV bolus or by direct IV**. Do not shake the vial. Do not dilute its contents.**

Cetuximab should be scheduled and administered every 14 days, if possible on the same day of the week. Cetuximab shall be administered 1 hour prior to starting chemotherapy. Premedication with an **antihistamine and corticosteroids** is recommended (≈ 30 min beforehand and by IV). The cetuximab infusion is administered over a period between 90 and 120 minutes and the maximum infusion rate must not exceed 2 ml/minute. The infusion line must be rinsed with a sterile 0.9% sodium chloride solution for injection, at the end of infusion.

Do not shake the vial, do not dilute its contents. Prepare the infusion using a suitable aseptic method. Cetuximab should be administered by an infusion pump or by a syringe pump. To obtain the recommended dose, multiple vials should be mixed using an aseptic method in an infusion container prior to administering the medicinal product. To prevent vacuum formation, a venting needle may be used. Cetuximab must not be mixed or diluted with other medicinal products, as no studies have been conducted on the physical or biochemical compatibility of cetuximab mixed with other agents.

After the cetuximab infusion, it is advised to keep the patient under observation for one hour. In patients exhibiting reactions to the infusion, a longer observation period may be required.

The vials must be stored in a refrigerator between 2 and 8°C. Do not freeze. Prepare under aseptic conditions and administer as soon as possible as the product contains no preservatives. It has been demonstrated that Cetuximab preparations in infusion containers, prepared under controlled conditions, are chemically and physically stable for up to 12 hours, at a temperature situated between 2 and 8°C and for up to 8 hours, at a controlled ambient temperature (between 20 and 25°C). It is not recommended to store Cetuximab in infusion containers and all unused portions of the solution should be discarded after 8 hours, if it has been left at a controlled ambient temperature, or after 12 hours, if it has been stored at a temperature situated between 2 and 8°C.

6.2 Packaging and labelling

The anti-VEGF monoclonal antibody **bevacizumab (Avastin®),** solution for infusion to be diluted to 25mg/ml in 4ml and/or 16ml vials, shall be prepared according to Good Manufacturing Practices (GMP) by ROCHE Laboratories.

Bevacizumab shall be packaged in boxes. Each vial contains 25 mg/ml of bevacizumab. The boxes shall contain the instructions for use of the product in French.

The boxes and vials shall be labelled as per Annex 13 of the Community Good Manufacturing Practice guidelines (revised and adopted in July 2003 by the European Commission).
The labels affixed on the treatment boxes shall contain the following information.

- Name and address and telephone number of sponsor
- Name of principal investigator
- Pharmaceutical form, name and dosage of product, administration route.
- Study reference.
- Batch number
- Number of vials and vial number
- The wording: "For clinical trial use only".
- Storage conditions.
- Instructions for use

The other treatments should be taken from the usual healthcare facility pharmacy stock.

6.3 Distribution, accounting and disposal

Bevacizumab shall be distributed to the various healthcare facility pharmacies by Roche Laboratories in accordance with Good Distribution Practices.

The healthcare facility pharmacist acknowledges receipt of all the shipments by returning a duly completed acknowledgement of receipt to the distributor.

The facility pharmacist shall set up an accounting system for dispensed, used or unused medicines and/or those returned by the patient according to the relevant procedures. The batch No. and the patient's initials shall be noted at the pharmacy.

The study medicines must be stored in a restricted-access, locked room and according to the manufacturer's recommendations.

The clinical research associate appointed by the sponsor shall check the accounts of the medicines supplied and ensure that an accounting form has been validated and signed by the facility pharmacist prior to any disposal request.

Bevacizumab shall not be disposed of by the investigation centre until authorised to do so by the Sponsor. Immediate disposal of the other products by the investigation centre shall be required for safety reasons. The investigation centre shall be able to dispose of these products once they have been dispensed provided that product traceability is guaranteed by comparing the dispensing register with the remaining inventory and the records of the quantities shipped, dispensed, returned and disposed of.

6.4 Treatment procedure

Patients having signed their consent form and complying with all inclusion and non-inclusion criteria shall be randomised into either:

ARM A: bevacizumab + fluoropyrimidine-based standard chemotherapy

ARM B: cetuximab + fluoropyrimidine-based standard chemotherapy

The treatment should commence within **7 days** after randomisation. It shall be continued until tumour progression or limiting toxicity.

All patients **must receive one of the standard chemotherapy regimens** for colorectal cancer treatment described below:

- mFOLFOX6:

Every 14 days:

- Oxaliplatin: 85 mg/m^2 in 120 min IV on day D1
- Folinic acid: 400 mg/m² (racemic) (or 200 mg/m² if L-folinic acid) in 2 hrs IV on D1 (concurrent with oxaliplatin) followed by
- 5-fluoro-uracil: 400 mg/m² by IV bolus on D1 followed by
- 5-fluoro-uracil: 2400 mg/m² by 46-hour IV infusion

or

- FOLFIRI:

Every 14 days:

- Irinotecan: 180 mg/m^2 in 90 min IV on day D1
- Folinic acid: 400 mg/m² (racemic) (or 200 mg/m² if L-folinic acid) in 2 hrs IV on D1 (concurrent with irinotecan) followed by
- 5-fluoro-uracil: 400 mg/m² by IV bolus on D1 followed by
- 5-fluoro-uracil: 2400 mg/m² by 46-hour IV infusion

All patients included in **arm A** shall receive, in addition to one of the standard chemotherapy regimens, **bevacizumab** administered before or after chemotherapy

- **5 mg/kg IV every 14 days**

Regarding Bevacizumab administered at 5 mg/kg/week every two weeks. The initial dose of bevacizumab shall be administered in 90 (±15) minutes. If the first infusion is well tolerated and there are no associated adverse events (fever or tremors), the second infusion may be administered in 60 (±10) minutes. If the infusion is well tolerated in 60 minutes, all subsequent administrations may be carried out in 30 (±10) minutes.

On the other hand, if the first infusion is poorly tolerated, the second shall be administered in 90 minutes. Premedication shall be set up according to local protocols.

The doses of bevacizumab must not be reduced, temporary or definitive discontinuation shall be implemented. "Missed" doses of bevacizumab shall not be replaced

All patients included in **arm B** shall receive, in addition to one of the standard chemotherapy regimens, **cetuximab** administered before or after chemotherapy, except for irinotecan (after chemotherapy)

- **500 mg/m²** administered by IV infusion every 14 days

Regarding cetuximab, allergic and/or hypersensitivity reactions may occur during or in the course of the cetuximab infusion. Prior to the cetuximab infusion, patients must receive premedication with an antihistamine and corticosteroids. This premedication is recommended for subsequent infusions

6.5 Toxicity and Dose adaptation

6.5.1 General instructions relating to discontinuing treatment

The toxicities shall be assessed and graded according to CTC AE V4 criteria (Appendix 5). The neurological toxicity shall be assessed and graded according the modified Levi scale (Appendix 4). The skin and ungueal toxicities shall be assessed and graded according to CTC AE V4 criteria (Appendix 5).

In the event of toxicity requiring the definitive discontinuation of a chemotherapy **drug**, bevacizumab or cetuximab, the treatment shall be retained with the other drugs.

In the event of toxicity requiring deferral of the chemotherapy treatment, the entire treatment shall be deferred to the same extent.

 In the event of definitive discontinuation of chemotherapy, bevacizumab and/or cetuximab shall be continued until disease progression except in the event of unacceptable toxicity.

 In the event of discontinuation of **chemotherapy and of the targeted therapy** > 6 weeks, the patient shall discontinue the 2nd Line Prodige 18 – Accord 22 protocol treatment

Event	Action
Arm A = bevacizumab	
Discontinuation of chemotherapy	Continue bevacizumab
Discontinuation of bevacizumab	Continue chemotherapy
bevacizumab deferred	- Do not defer the administration of the chemotherapy treatment - No reduction in the bevacizumab dose is authorised
Arm B = cetuximab	
Discontinuation of chemotherapy	Continue cetuximab
Discontinuation of cetuximab	Continue chemotherapy
cetuximab deferred	- Do not defer the administration of the chemotherapy treatment

The dosage adjustments associated with the onset of toxicities are described below for each type of treatment.

Where several toxicities differing in grade and severity occur at the same time, the dose modifications shall be made according to the greatest applicable dose reduction.

6.5.2 Toxicities associated with bevacizumab

There shall be **no modifications of the doses of bevacizumab** in the course of this study, unless the patient's weight varies by more than 10%; in this case, the dose shall be recalculated.

Procedure to follow in the event of grade 3/4 events associated with bevacizumab
- 1st occurrence of event: temporary discontinuation of bevacizumab until event returns to a grade ≤1
- 2nd occurrence of event: definitive discontinuation of bevacizumab

For subsequent grade 4 events (associated with bevacizumab or not)
- Grade 4 febrile neutropenia: temporary discontinuation of bevacizumab until return to a grade ≤1 followed by resumption
- Grade 4 thrombocytopenia: temporary discontinuation of bevacizumab until return to a grade ≤1 followed by resumption

Definition discontinuation of bevacizumab in the following cases:

- Any grade:
  - Arterial thromboembolic accidents
  - Gastrointestinal perforation
  - Tracheo-oesophageal fistula
  - Non-gastrointestinal fistula

- Allergic reactions to bevacizumab
- Pulmonary bleeding/haemoptysis
- CNS bleeding

- Grade 3/4:
  - Bleeding
  - Left ventricular dysfunction
  - Bowel obstruction
  - 2nd occurrence of grade 3/4 event

- Grade 4:
  - Hypertension (hypertensive episode)
  - Proteinuria (nephrotic syndrome)
  - Reversible posterior leucoencephalopathy syndrome

Missed doses of bevacizumab shall not be replaced.

Reactions to infusion:

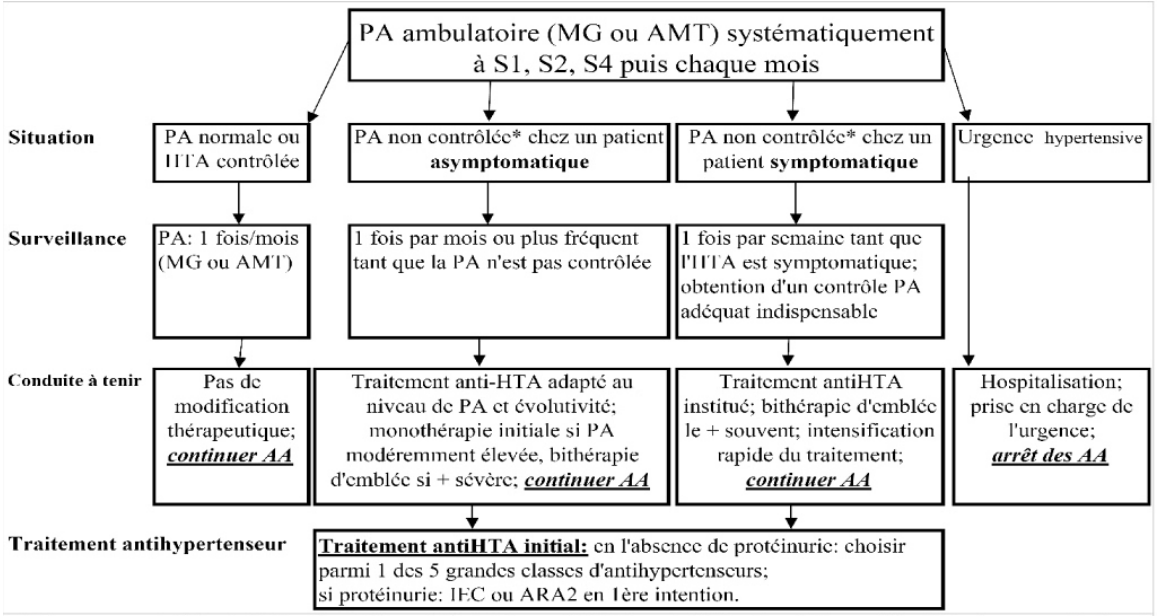
The bevacizumab infusion must be discontinued in the event of a severe reaction and suitable medical treatment must be put in place.

Arterial hypertension:

A higher incidence of arterial hypertension has been observed in patients treated with bevacizumab. These cases were generally treated with oral antihypertensive agents such as angiotensin converting enzyme inhibitors, beta-blockers, diuretics and calcium channel blockers.

Patients should be monitored with frequent measurements of their blood pressure in order to detect the onset or worsening of hypertension. Follow-up shall be recommended. Blood pressure measurements should be made after resting for at least 5 minutes. A second verification measurement should be performed if the initial value is ≥ 140 mmHg for the systolic pressure and/or ≥ 90 mmHg for the diastolic pressure.

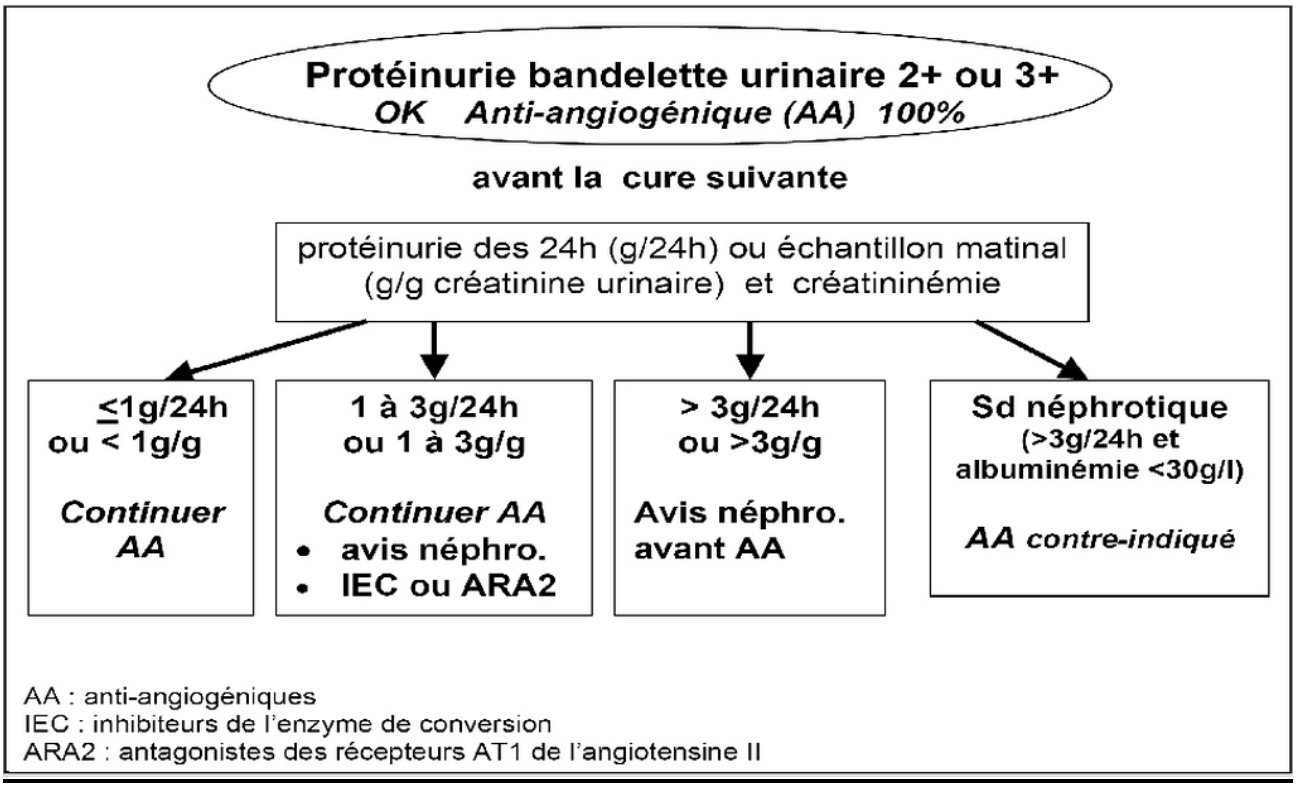
BP management: TNCD 16/12/2009 (www.tncd.org)



*PA non contrôlée: >135 et/ou 85 mmHg (PA en AMT) ou ≥ 140 et/ou 90 mmHg (PA de consultation)
MG: médecin généraliste
AMT: auto-mesure tensionnelle
AA: anti-angiogéniques
S1, S2, S4: semaine 1, 2 et 4

Proteinuria: TNCD 16/12/2009 (www.tncd.org)

The administration of bevacizumab should be discontinued in patents presenting with grade 4 proteinuria (nephrotic syndrome).



AA : anti-angiogéniques
IEC : inhibiteurs de l'enzyme de conversion
ARA2 : antagonistes des récepteurs AT1 de l'angiotensine II

Digestive perforation:

Bevacizumab treatment must be discontinued definitively in the event of the onset of digestive perforation.

Wound healing complications:

Bevacizumab must not be initiated within 28 days following a major surgical procedure or until the surgical wound has fully healed. In patients presenting with a wound healing complication under bevacizumab treatment, bevacizumab must be discontinued until the wound has fully healed. Bevacizumab treatment must be discontinued at least 28 days prior to an elective surgical procedure.

Thrombosis/embolism:

A grade as per NCI-CTC criteria shall be attributed to all toxicity signs. Bevacizumab treatment should be temporarily or definitively discontinued in patients presenting with grade 3 or 4 thrombosis or embolism and the recommended actions are as follows:

- The administration of bevacizumab should be discontinued definitively in patients presenting with an arterial thromboembolic accident.
- Grade 3 venous thrombosis or grade 4 asymptomatic thrombosis: discontinue the study treatment (bevacizumab). Discontinue the administration of bevacizumab until the end of the anticoagulant treatment if the planned duration of this treatment is ≤ 2 weeks. If this duration is ≥ 2 weeks, discontinue the administration of bevacizumab for 2 weeks and then resume administration during the anticoagulant treatment at a therapeutic dose once the following criteria have been met:
  - The anticoagulant dose should be stable and, in the case of warfarin, the INR should be situated in the target range (usually between 2 and 3) before resuming the study treatment (bevacizumab). In any case, a low molecular weight heparin anticoagulant treatment is highly recommended.
  - The patient must not have presented with a grade 3 or 4 bleeding event from the time of inclusion in the study.
  - The patient should not exhibit any symptom of a tumour invading or bordering on a major blood vessel at any of the previous scans.
- Grade 4 symptomatic thrombosis: The bevacizumab treatment shall be discontinued definitively.

Bleeding:

In patients presenting with grade 3 or 4 bleeding, the bevacizumab treatment shall be discontinued definitively.

Overdosage:

The highest dose studied in clinical practice (20 mg/kg by the IV route) has been associated with severe migraine in several patients.

Modification of bevacizumab administration in the event of adverse events

AE/NCI TCAE grade	Procedure to follow
Hypertension	
Grade 1	No modifications of bevacizumab treatment
Grade 2 or 3	Discontinue bevacizumab temporarily and place the patient on antihypertensive treatment or boost the antihypertensive treatment. If the hypertension is controlled (≤ 150 mmHg/100 mmHg) with treatment, resume bevacizumab
Grade 4	Discontinue bevacizumab definitively
Signs of Reversible Posterior Leucoencephalopathy Syndrome (RPLS)	
Any grade (confirmed by MRI)	Discontinue bevacizumab
CNS bleeding	
Any grade	Discontinue bevacizumab
Pulmonary bleeding	
Any grade	Discontinue bevacizumab
Non-pulmonary, non-CNS bleeding	
Grade 1	No dose modifications.
Grade ≥ 2	Discontinue bevacizumab
Venous thrombosis	
Any grade	Discontinue bevacizumab for 2 weeks and resume during the treatment period at a therapeutic dose
Arterial thromboembolic event (angina, myocardial infarction, ischaemic heart attack, stroke or any other arterial thromboembolic event)	
Any grade	Discontinue bevacizumab
Proteinuria	
Grade 1 or 2	No dose modifications
Grade 3	Discontinue bevacizumab until resolution to a Grade≤ 2
Grade 4 (nephrotic syndrome)	Discontinue bevacizumab
GI perforation	
Grade ≥ 2 (Requiring medical or surgical intervention)	Discontinue bevacizumab
Bowel obstruction	
Grade 1	Retention of patient in study for partial obstruction NOT requiring medical/clinical intervention.
Grade 2	Discontinue bevacizumab for partial obstruction requiring medical/clinical intervention. The administration of the treatment shall resume once fully resolved.
Grade 3 or 4	Discontinue bevacizumab in the event of total obstruction. If a surgical procedure is required, the patient shall resume treatment after the wounds have fully healed, subject to the investigator's judgement.
Wound dehiscence requiring medical or surgical treatment (if the wound originates from an incision of a cavity)	
Any grade	Discontinue bevacizumab
Left ventricular systolic dysfunction	
Grade 1 or 2	No dose modifications
Grade 3	Discontinue bevacizumab until resolution to a grade ≤ 1
Grade 4	Discontinue bevacizumab
Fistula	
Any other Grade 3/4 events potentially associated with bevacizumab according to the investigator	
Grade 3	Discontinue bevacizumab until resolution to a grade ≤ 1.
Grade 4	Discontinue bevacizumab

6.5.3 Toxicities associated with cetuximab

The guidelines relating to cetuximab treatment modifications in the event of toxicity, based on the experience acquired in Research and Development and classified according to CTCAE (National Cancer Institute-Common Terminology Criteria for Adverse Events, Version 4.0) criteria (Appendix 5), are summarised in the sections below.

Cetuximab dosage reductions are **definitive**.

a- Specific infusion-related allergic/hypersensitivity reactions:

In the event of specific infusion-related allergic or hypersensitivity reactions, the investigator must treat the patient based on the latest treatments available.
Symptoms generally occur during the 1st injection and within one hour following the end of infusion. These symptoms may last for several hours and appear during subsequent infusions

Prior to each infusion of cetuximab, it is recommended to administer **premedication with an antihistamine + corticosteroids** so as to reduce the risks of specific infusion-related reactions. This **premedication with antihistamines and corticosteroids (Solumedrol 120 mg and anti-H1 IV) is mandatory prior to the first 3 infusions of cetuximab**. The anti-H1 premedication may be discontinued from the fourth cycle in the absence of specific infusion-related reactions.

A local preventive systemic antibiotherapy treatment (tetracycline type such as doxycycline 100 mg/day) may be envisaged to reduce the frequency and intensity of skin toxicity
The guidelines relating to cetuximab treatment modifications in the event of specific infusion-related allergic reactions are, also, based on the experience acquired with cetuximab treatments. They are summarised in the table below:

NCI -CTCAE Reaction Grade	Treatment
Grade 1 Transient eruption or rash; drug-induced fever < 38°C	Reduce the cetuximab infusion rate by 50% and monitor the outcome closely. If the reaction persists despite this first reduction, proceed as follows for subsequent rate reductions - 1st infusion: reduce the infusion flow rate by 50%, giving a total infusion time of 4 hours. - 2nd infusion: reduce the infusion flow rate by 50%, giving a total infusion time of 3 hours. If the anaphylactic reaction persists, reduce the infusion rate further by 25% for a total infusion time of 4 hours. - 3rd subsequent infusions: reduce the infusion flow rate by 50%, giving a total infusion time of 3 hours. If the anaphylactic reaction persists, reduce the infusion rate further by 50% for a total infusion time of 4 hours The total infusion time of cetuximab 500 mg/m² must not exceed 4 hours.
Grade 2 Eruption; rash; urticaria; dyspnoea; drug-induced fever ≥ 38°C occurring shortly after administering the treatment	Discontinue cetuximab infusion. Bronchodilator, oxygen treatment, etc., according to clinical status. Once the status has returned to normal or decreased to grade 1, continue infusion at 50% of the initial rate, monitoring the patient closely. The extension of the infusion times as described for Grade 1 management may be applied for such cases. The total infusion time of cetuximab 500 mg/m² must not exceed 4 hours.
Grade 3 or grade 4 Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related oedema/angioedema; hypotension. Anaphylaxis; Non-susceptible to discontinuation of infusion and/or to symptomatic treatments; recurrent after initial improvement, hospitalisation and sequelae	Discontinue cetuximab infusion immediately and remove infusion. Treatment with epinephrine, bronchodilators, anti-histamines, glucocorticoids, vasopressors, oxygen, etc., according to clinical status. Discontinue cetuximab treatment immediately with no subsequent further treatment. No subsequent further treatment
Grade 4 Anaphylaxis Life-threatening consequences; urgent intervention indicated	Discontinue cetuximab treatment immediately with no subsequent further treatment.

Resumption of treatment after specific infusion-related reactions

Once the cetuximab infusion rate has been lowered due to this type of allergic or hypersensitivity type toxicity, this rate shall be maintained for subsequent administrations of cetuximab.

. If a second episode of specific infusion-related allergic or hypersensitivity reactions occurs while the infusion rate has already been reduced, the infusion must be stopped and the cetuximab treatment discontinued definitively.

. If a grade 3/4 specific infusion-related allergic or hypersensitivity reaction is reported, the cetuximab must be discontinued definitively regardless of the time of onset during the study.

b- Electrolyte imbalances

Cases of progressive decline in the serum magnesium concentration are frequent and may give rise to severe hypomagnesaemia. The hypomagnesaemia is reversible after discontinuing cetuximab. Moreover, hypokalaemia may also be induced by diarrhoea. Hypocalcaemia may also occur; in particular, in association with platinum salt-based chemotherapy; the frequency of severe hypocalcaemia may be increased.

It is recommended to assay serum electrolyte concentrations prior to cetuximab treatment, and also regularly during treatment. Electrolyte supplementation is recommended if required.

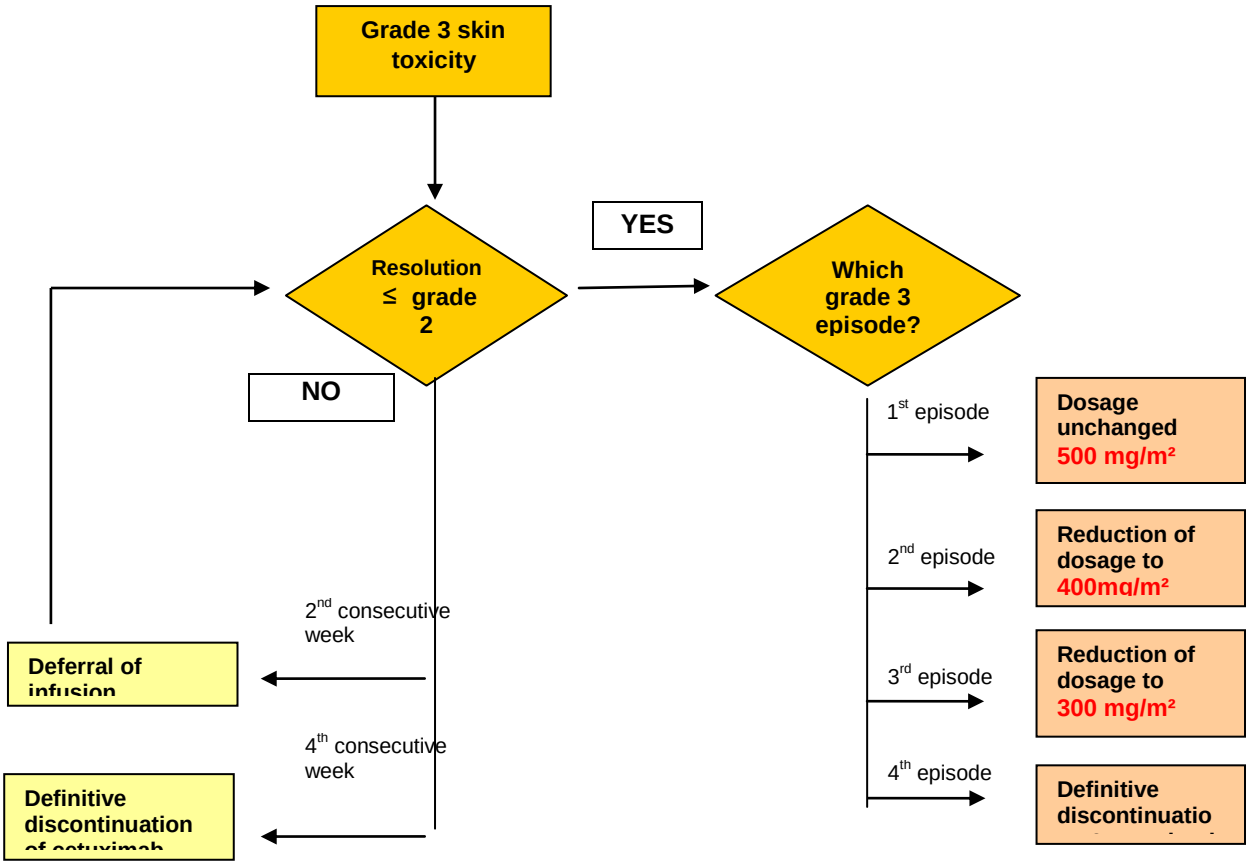
c- Skin toxicity

- **Grade 1 or 2**: a local anti-acne or anti-rosacea treatment (e.g. benzoyl hydroxide, erythromycin) or systemic antibiotherapy (tetracycline type such as doxycycline 100 mg/day) may be envisaged. In the event of pruritus, an oral antihistamine treatment is advised. In the event of dry skin, the use of emollient creams is beneficial. Skin fissures may occur in the event of dryness; these may be treated with dressings.
- **Grade ≥ 3**: Dermatological therapeutic advice is required.

  If the toxicity grade decreases to grade 2 or less, cetuximab treatment may be resumed. In the event of the **onset of a second or third grade 3 toxicity episode**, the cetuximab treatment may be deferred once again for a maximum period of 2 consecutive weeks with concomitant reduction of the dosage to 400 mg/m² and 300 mg/m².

  Once the cetuximab dosage has been reduced, it shall be retained for subsequent infusions. Cetuximab treatment must be discontinued definitively in cases where more than one infusion has not been administered or if a fourth grade 3 episode occurs despite reductions in the cetuximab dosage (see figure below). However, cetuximab may only be discontinued immediately and definitively on the investigator's advice, insofar as it is deemed necessary for the patient.

  The cetuximab dose adaptation procedures in the event of the onset of grade 3 skin toxicity are summarised in the figure below.



Definitive or temporary discontinuation of cetuximab treatment

The cetuximab treatment may also be deferred or discontinued if the patient develops an intercurrent disease (e.g. infection).

After the discontinuation, the patient may resume the cetuximab treatment at a dosage of 500 mg/m² every 2 weeks or at the last dosage administered prior to discontinuing the treatment if dose reductions had already been envisaged.

Once the cetuximab dosage has been reduced, it shall be retained for subsequent infusions.

In the event of the cetuximab treatment being deferred or discontinued, the concomitant chemotherapy must be continued according to the terms described in this protocol.

TNCD recommendation 16/12/2009 (www.tncd.org)

Local preventive treatment must be envisaged to reduce skin toxicity frequency and intensity:

-emollients, sun block, cleansing with dermatological bar, sun avoidance

- tetracycline such as doxycycline (e.g. Tolexine ® Gé 100 mg 1 tab or 2 tab per day with meals)

Excessive sun exposure, insufficient skin hydration, or the use of gels or lotions with irritant alcohol-based excipient are aggravating factors.

Curative treatments must be set up in the event of acneiform reactions:

- Minor forms: emollient + local metronidazole

Dexeryl® cream 1 to 2 applications daily after cleansing

Rozex® cream 2 applications every morning and evening

- Inflammatory forms on the torso: local benzoyl peroxide

Cutacnyl® gel 10% 1 application every evening

- Intermediate forms: local metronidazole, cyclines per os, + local class III corticosteroid

Dexeryl® cream 1 application every evening

Rozex® cream 2 applications every morning and evening

Tolexine ® Gé 100 mg 1 tab per day with meals for 1 months followed by 1 x 50 mg tab per day, repeatable over several months.

Diprosone® cream 1 application every evening

- Severe (superinfection) or atypical forms => DERMATOLOGICAL ADVICE.

discontinuation of anti-EGFr treatment discussed among dermatologist, oncologist and patient. Swabbing with bacteriological and viral culture testing. Topical antibiotherapy (fusidic acid: Fucidine® cream) with or without per os targeting Staphylococcus aureus according to the number of lesions, such as penicillinase-resistant penicillins (oxacillin) or synergistin (pristinamycin)

- Skin fissures: oily creams (Cold Cream® or Codex petroleum jelly) or healing ointments not subject to reimbursement (e.g. Bepanthen® or Avibon®), hydrocolloidal dressings (e.g. Comfeel® thin)

In the event of Hypertrichosis: cut eye-lashes in the event of ocular discomfort, hair removal in case of cosmetic or psychological effect

In the event of Perionychitis = "pseudo-paronychia"

-*Preventive treatments*: pedicure treatments prior to commencing treatment, do not cut nails close to corners; good hygiene, prevent microtrauma (excessively tight shoes, excessively high heels)

-*Curative treatments*: antiseptics (e.g. Betadine® scrub 4% or Dakin wash once daily or Betadine 10% gel). If painful: antiseptics + local class IV corticosteroid (example of prescription below):

- Biseptine® spray 1 application per day followed by / Dermoval® cream – thick layer followed by occlusive dressing /- Compresses 10 x 10 1 pack of 100 Omnifix 1 pack in case of superinfection: dermatological advice, in case of painful vegetative appearance (pyogenic granuloma): daily application of silver nitrate (pencil)

Magnesaemia:

TNCD 16/12/2009 (www.tncd.org) recommends magnesium monitoring by means of assays.

Intravenous supplementation must be set up

- in case of hypomagnesaemia < 1.2 mg/dl and/or symptomatic hypomagnesaemia with magnesium sulphate:
- in case of hypomagnesaemia between 1.2 and 0.9 mg/dL = 4 g IV in 2 hours at each cycle
- in case of hypomagnesaemia < 0.9 mg/dL = 8 g IV in 4 hours/day or every 2 days until normalisation

6.5.4 Chemotherapy-induced toxicities

6.5.4.1 Oxaliplatin-induced toxicities

To evaluate the assessable toxicity, the patients must have received at least one treatment administration.

-Extravasation:
Severe oxaliplatin extravasation-related reactions have been reported. The general guidelines in the event of extravasation are as follows:
- Discontinue the infusion immediately,
- Do not remove the needle or catheter,
- Aspirate the maximum amount of infiltrated drug via the same needle,
- Apply ice on the infiltrated area for 15 to 20 minutes every 4 to 6 hours for 72 hours,
- Local corticotherapy,
- check the infiltrated site regularly on subsequent days, so as to check if any treatment is required. Do not hesitate to seek surgical advice if in doubt

- Intolerance reactions to oxaliplatin (between 1 and 10%):
Skin rash (particularly urticaria), conjunctivitis, rhinitis, pharyngolaryngeal dysaesthesia

Are to be treated as follows:

- Immediate discontinuation of oxaliplatin infusion
- Infusion of polaramine/corticosteroids
- Infusion of filling solution (macromolecules) if required.
- Patient discharge on same day or on following day based on recovery
- Report an SAE using the form included in the CRF

Optionally resume the oxaliplatin infusion on the same day at a lower rate in the event of full recovery.

At the next cycle, resume oxaliplatin treatment with the following adaptations:

- Infusion of polaramine prior to oxaliplatin
- Infusion of oxaliplatin over 4 to 6 hours

- Anaphylactic reactions including bronchospasm, chest pain sensation, angioedema, hypotension, etc.

Are to be treated as follows:

Immediate **and definitive** discontinuation of oxaliplatin infusion
Infusion of polaramine/corticosteroids
Infusion of filling solution (macromolecules) if required.
Report an SAE using the form included in the CRF

If oxaliplatin is discontinued due to neurotoxicity, the other study treatments shall be continued alone. Oxaliplatin may be reintroduced in the event of a first grade 3 toxicity episode and if the toxicity grade is ≤ 2.

Grade 3-4 acute **laryngopharyngeal dysaesthesia syndrome** reported with oxaliplatin treatments with an incidence of 1 to 2%, generally starts in the hours following administration and frequently occurs following exposure to cold. This syndrome is characterised by subjective sensations of dysphagia and dyspnoea without signs of respiratory distress (hypoxia, laryngospasm, bronchospasm). Contracture of the jaw, lingual dysaesthesia sometimes followed by dysarthria and chest tightness have also been observed. Although antihistamines and bronchodilators may be administered in these scenarios, this symptomatology is rapidly reversible, even in the absence of any treatment.
Extending the infusion time in subsequent cycles helps lower the incidence of this syndrome. Subsequent oxaliplatin doses should be administered by longer infusion, of approximately 6 hours. Exposure to cold should be strictly avoided.

- Neurological toxicity shall be assessed using the Levi scale **(appendix No. 4**):
The limiting toxicity of oxaliplatin is neurological. It consists of sensory peripheral neuropathy characterised by dysaesthesia and/or paraesthesia of the extremities, accompanied by cramps or not, frequently triggered by the cold. These symptoms appear in 85 to 95% of patients treated. The duration of these symptoms, which generally regress between treatment cycles, increases with the repetition of the latter. The onset of pain and/or functional discomfort requires, depending on the duration of the symptoms, adjustment of the dose, or even discontinuation of the treatment. This functional discomfort, which includes difficulties carrying out fine motor tasks, is a possible result of sensory impairment. The risk of the onset of functional discomfort for a cumulative dose of approximately 800 mg/m² (i.e. 10 cycles) is 15% or less. The neurological symptomatology frequently improves on discontinuing the treatment.

Toxicity	Grade	Duration of toxicity		
		1 to 7 days	> 7 days	Persistence between cycles[a]
Paraesthesia/dysaesthesia[b] not causing functional discomfort	1	No change	No change	No change
Paraesthesia/dysaesthesia[b] causing functional discomfort, but not interfering with day-to-day activity	2	No change	Reduce to 65 mg/m²	Temporary discontinuation until toxicity returns to a grade ≤ 1
Paraesthesia/dysaesthesia[b] with pain or functional discomfort interfering with day-to-day activity	3	Reduce to 65 mg/m² Or 100 mg/m² d	Temporary discontinuation until toxicity returns to a grade ≤ 1	Discontinuation of treatment
Incapacitating or life-threatening paraesthesia/dysaesthesia	4	Discontinuation of oxaliplatin	Discontinuation of oxaliplatin	Discontinuation of oxaliplatin
ACUTE (during or after the 2 hours of infusion), Laryngopharyngeal dysaesthesia		Increase the subsequent infusion time to 6 hours[c]	N/A	N/A

[a] Unresolved at the start of the next cycle
[b] Not cold-induced
[c] Possible pre-treatment with benzodiazepines
[d] if the oxaliplatin dose is 100 mg/m² at the start, dose reduction = 65 mg/m² if the oxaliplatin dose is 130 mg/m² at the start, dose reduction = 100 mg/m²

- Haematological toxicity:

In the event of haematological impairment (neutrophils <1.5x10^9/L or platelets <50x10^9/L), defer the administration of the next cycle until acceptable values have returned. A full blood count must be performed before initiating an oxaliplatin treatment and prior to each new cycle. Patients must be informed of the risk of the occurrence of diarrhoea/vomiting, mucositis/stomatitis and neutropenia, after administering oxaliplatin and 5-fluorouracil, and contact their attending physician immediately in order to receive suitable care. In the event of the onset of mucositis/stomatitis with or without neutropenia, the following administration shall be deferred until the mucositis/stomatitis has returned to a grade less than or equal to 1 and/or a neutrophil level ≥ 1.5x10^9/l. As oxaliplatin is associated with 5-fluorouracil (with or without folinic acid), the toxicities specific to 5-fluorouracil must be the subject of the standard dose modifications recommended for this drug. The occurrence of grade 4 diarrhoea, grade 3 or 4 neutropenia (neutrophils <1x10^9/l) or grade 3 or 4 thrombocytopenia (platelets <50x10^9/l) shall require, in addition to adaptation of the 5-fluorouracil dose, a reduction in the oxaliplatin dose from 85 to 65mg/m² (metastatic treatment).

In the event of the onset of unexplained respiratory symptoms, such as an unproductive cough, dyspnoea, crepitant rale or radiological pulmonary infiltrates, the oxaliplatin treatment must be discontinued, until the pulmonary exploration has ruled out interstitial pneumopathy.

6.5.4.2 Irinotecan-induced toxicities

Haematological toxicity:

Weekly full blood count monitoring is recommended during Irinotecan treatment. Febrile neutropenia (temperature >38°C and neutrophil count <1000/mm^3) requires urgent treatment in a hospital setting, with broad-spectrum antibiotics administered by the IV route.
In patients who have had severe haematological toxicity, the dose must be reduced. Furthermore, **secondary** prophylaxis with Granocyte 34® may be set up in the event of:

- grade 4 neutropenia
- febrile neutropenia
- neutropenia resulting in cycle deferral (N count < 1.5 10^9/L on D15 or D21 according to treatment arm).

In these cases, Granocyte 34® shall be set up for all subsequent cycles at a dose of 150 µg/m^2/day.
For both arms, Granocyte 34® shall be set up from D6 to D12.
For patients over 70 years of age, as the risk of myelosuppression increases, primary prophylaxis with Granocyte 34® is possible.

Digestive toxicity:

-Diarrhoea

From the first loose stools, the patient must drink plenty of electrolyte-enriched beverages and commence suitable antidiarrhoeal treatment immediately. For this, the antidiarrhoeal treatment shall be prescribed in the department where Irinotecan was administered. Upon discharge from the hospital, the patients should procure the prescribed medication to be able to treat diarrhoea as soon as it occurs.

The antidiarrhoeal treatment currently recommended consists of high doses of loperamide (4 mg for the first dose followed by 2 mg every 2 hours). This treatment must be continued for at least 12 hours after the last liquid stools, without modifying the dosage. Under no circumstances should loperamide be administered, at this dosage, for more than 48 consecutive hours, due to the risk of paralytic ileus.

Preventive broad-spectrum antibiotherapy may be associated with the antidiarrhoeal treatment in cases of diarrhoea concomitant with severe neutropenia (neutrophil count <500/mm^3).
Hospitalisation, associated with antibiotherapy, is recommended in the following cases to control diarrhoea:

- Diarrhoea accompanied by fever,
- Severe diarrhoea (requiring parenteral rehydration),
- Persistent diarrhoea after 48 hours of treatment at a high loperamide dose.

Loperamide must not be administered for prophylactic purposes, even to patients presenting with delayed diarrhoea following prior cycles.
In patients presenting with severe delayed diarrhoea, a reduction in the dosage is recommended for subsequent cycles.

- Nausea and vomiting

A prophylactic antiemetic treatment is recommended prior to each administration of Irinotecan. Nausea and vomiting have been frequently reported.
Patients in whom vomiting is associated with delayed diarrhoea must be hospitalised without delay

- Acute cholinergic syndrome

If acute cholinergic syndrome occurs (defined by early-onset diarrhoea and a set of symptoms such as excessive sweating, abdominal cramps, watery eyes, myosis, and hypersalivation), atropine sulphate (0.25 mg subcutaneously) must be administered except in the case of its clinical contraindications. Precautions must be taken for asthmatic patients.
If acute cholinergic syndrome was observed following the first administration, the prophylactic use of atropine sulphate is recommended for subsequent administrations of Irinotecan.

Respiratory disorders:

Cases of interstitial lung disease with pulmonary infiltrates are relatively infrequent under Irinotecan treatment. Interstitial lung disease may be fatal. The risk of developing interstitial lung disease may be promoted by the concomitant administration of pneumotoxic drugs, radiotherapy, and the administration of growth factors. In patients presenting with risks factors, the onset of respiratory symptoms should be monitored closely before and during Irinotecan treatment.

6.5.4.3 5-FU-induced toxicity

Digestive toxicity: The onset of **stomatitis** and particularly of diarrhoea must result in **discontinuation of treatment** until the symptoms clear; the same applies in the event of **gastrointestinal ulceration formation or the onset of bleeding** regardless of the location.

Haematological toxicity: The **treatment shall be discontinued** in the event of granulopenia below 2000 white blood cells per mm^3 or thrombocytopenia below 80,000 platelets per mm^3.

Cardiac toxicity: The onset of **heart symptoms must result in the immediate discontinuation** of the continuous 5-FU infusion. In this case, its reintroduction must be not be envisaged.

6.6 Concomitant treatments

Antitumour treatments other than the study treatments are not permitted. The use of other chemotherapeutic, biological agents or experimental drugs for colorectal cancer is not permitted during the treatment and follow-up periods as long as the patient does not display recurrence.

a- Medicinal products potentially interacting with bevacizumab

Coumarin derivatives, heparin, aspirin and NSAIDs

The most severe toxicities observed with bevacizumab to date are bleeding, thrombosis and gastrointestinal perforations. The use of these medicinal products must be restricted. Furthermore, the administration of 5-FU has also been associated with bleeding and intestinal perforations.
Patients requiring oral administration of an active dose of coumarin derivative anticoagulants (INR >1.5) or heparin thrombolytic agents or chronic administration of aspirin (>325 mg/day) or of non-steroidal anti-inflammatory drugs inhibiting platelet function used to treat chronic inflammatory diseases shall not be included in the study (see inclusion and non-inclusion criteria).
The administration of low doses of coumarin derivatives, heparin, low molecular weight heparin is permitted, as are low doses of aspirin (<325 mg/day), the occasional administration of non-steroidal anti-inflammatory drugs, or of non-steroidal anti-inflammatory drugs inhibiting platelet function. Patients treated with an oral coumarin derivative must undergo regular monitoring of their clotting (INR), the anticoagulant dose should be adapted according to this response.

In patients presenting with a venous thromboembolic accident during the trial, active-dose anticoagulant treatment is permitted, and the data relating to the anticoagulant treatment (including the dose) shall be compiled in the case report form.
In patients treated with active doses of oral coumarin derivatives for a thromboembolic accident occurring during the study, the INR shall be monitored at least every two days in the first week of treatment, and at least twice weekly during subsequent weeks until a stable INR is obtained, then, at least once every three weeks when the weekly dose has been established and the INR stabilised at this dose.

b- Main medicinal products potentially interacting with irinotecan

- CYP3A4 inhibitors (such as cimetidine, macrolide class antibiotics (azithromycin, clarithromycin, erythromycin), azole antifungals (fluconazole, ketoconazole, itraconazole), grapefruit juice, and calcium channel blockers inhibiting CYP3A4 (verapamil, diltiazem, nifedipine)) may increase the toxicity of irinotecan. Such an interaction has been observed in cancer patients receiving irinotecan and ketoconazole, a powerful CYP3A4 inhibitor, concomitantly.
- Exposure to fluoroquinolones, such as ciprofloxacin or norfloxacin, may be increased in patients with impaired renal function following dehydration or colorectal cancer complications. In these patients, the concomitant administration of irinotecan and fluoroquinolone class antibiotics, that inhibit CYP3A4, could increase the toxicity of irinotecan.
- Moreover, the concomitant administration of irinotecan and CYP3A4 inducing agents (such as carbamazepine, phenobarbital, phenytoin, glucocorticosteroids and St. John's wort) could have an adverse effect on the treatment outcome. Such an interaction has been observed in cancer patients receiving irinotecan and St. John's wort, and irinotecan and phenytoin, concomitantly.

c- Main medicinal products potentially interacting with 5-FU

- Metronidazole: concomitant administration of metronidazole may increase the toxicity of 5-FU.
- Allopurinol (Zyloric®): concomitant administration should be avoided (loss of efficacy of 5-FU).

Concomitant medications shall be avoided, with the exception of analgesics, chronic treatments for pre-existing medical conditions, or those necessary if the patient is in a life-threatening situation.

Any other associated treatment including steroids such as antiemetics or any premedication with haematopoietic factors, proteins and any procedure, etc. not excluded from the protocol shall be left up to the judgement of the investigator and must be compiled in the case report form.

Oesophagitis: treated with local analgesics (xylocaine) or systemic analgesics (morphine derivatives), IV corticosteroids, antifungals.
Skin toxicity: prevention by wearing cotton underwear; treatment with moisturising ointments, local treatments (aqueous eosin in case of ulcerations). Topical corticosteroids are not recommended. Advise the patient to minimise sun exposure during Cetuximab treatment and for a period of two months after the administration of the final dose of Cetuximab.
Mucositis (mouth ulcers): prevention through dental care and oral hygiene; treatment by applying petroleum jelly on the lips, mouthwashes with aspirin, tetracyclines, metronidazole or antifungals.
Nausea, vomiting: prevention with anti-5HT3 + corticosteroids; treatment with metoclopramide, anti-5HT3, corticosteroids, Dogmatil®, Largactil®.
Diarrhoea: treatment with loperamide. The use of laxatives is not recommended, as they can exacerbate diarrhoea.
Constipation: treatment with osmotic laxatives, Duphalac®, Importal®

Haematopoietic factors (Granocyte 34 ®): may be administered according to the centre's usual practices and international guidelines.
Alopecia: scalp cooling to limit hair loss according to investigation centre.

7. PATIENT INCLUSION AND FOLLOW-UP ASSESSMENT

The monitoring of patients from the date of inclusion to the end of the study and the schedule of patient assessment are described in **appendix 1**.

The disease status shall be determined according to the modified RECIST V1.1 scale (Appendix 3).
To assess the efficacy of the treatment, it is essential that the same imaging technique (**CT scan of the chest, abdomen and pelvis)** be used for all tumour assessments for the same patient. It is also recommended for optimum assessment that these examinations be carried out in the same centre. It is therefore requested that a CT scan be rescheduled for patients at inclusion if this examination was performed in another centre.

The starting point = T0 of all assessments and follow-up is the RANDOMISATION date

7.1 Inclusion assessment

Patients eligible for the trial who have signed their consent form should undergo a clinical examination and a biological assessment within 7 days prior to randomisation.

- **Clinical examination**
  - Medical history and disease history
  - Clinical examination (weight, height and body surface, BP),
  - ECOG performance index (appendix 2),
  - ECG

- **Imaging examinations** (performed within 28 days prior to randomisation)
  - CT scan of the chest, abdomen and pelvis.
  - Brain scan in the event of suspected brain metastases
  - Bone scan in the event of suspected bone metastases

  Important: the examination carried out at inclusion must be the same as that carried out at subsequent tumour assessments. It is necessary and of prime importance to define the primary tumour targets accurately and monitor them so as to evaluate the primary assessment criteria according to RECIST v1.1.

- **Laboratory tests**
  - Blood electrolyte composition analysis (calcium, potassium, magnesium, sodium, bicarbonate, proteins, albumin)
  - Liver function (total and conjugated bilirubin, ALAT, ASAT, PAL, γGT, LDH)
  - Kidney function (creatinine clearance as per Cockcroft-Gault formula, creatininaemia, urea),
  - Full blood count and coagulation: FBC, platelets,
  - Tumour marker: ACE,
  - Pregnancy test,
  - Urine strip and, based on result, 24-h proteinuria,

- **Quality of life questionnaire**
  - EORTC QLQ – C30 (appendix 7 and 8)
    - **BEFORE** randomisation
    - **BEFORE** 1st Cycle

7.2 Patient follow-up during treatment

Patients shall be seen **every two weeks.** Patients must be seen for a consultation immediately prior to starting a new cycle, **until disease progression**.
According to the symptoms, further consultation visits may be required.

- **Clinical examination**
  - Clinical examination (including weight, BP),
  - ECOG performance index (appendix 2),
  - Assessment of tolerance as per CTCAE v4.0 (appendix 5), Levi scale (appendix 4), and check for recovery from any toxicities at baseline or grade ≤ 1 (except alopecia)

- **Laboratory tests**

  - Blood electrolyte composition analysis (calcium, potassium, magnesium, sodium, bicarbonate, protein, albumin)
  - Liver function (total and conjugated bilirubin, ALAT, ASAT, PAL, γGT, LDH)
  - Kidney function (creatinine clearance as per Cockcroft-Gault formula, creatininaemia, urea),
  - Full blood count and coagulation: FBC, platelets,
  - Tumour marker: ACE,
  - Proteinuria (on urine strips) for arm A only

All tests detecting treatment-induced toxicity must be repeated periodically until the toxicity has reversed or until it is deemed irreversible.

7.3 Tumour assessment

This assessment shall be performed every 6 weeks, until disease progression, whether

the treatment is administered or not

Assessments shall be carried out every 6 weeks even in cases of cycle deferral.

- **Laboratory test**
  - Tumour marker: ACE

- **Imaging examination**
  - CT scan of the chest, abdomen and pelvis.
  - Brain scan in the event of suspected brain metastases
  - Bone scan in the event of suspected bone metastases

Important: the imaging carried out must be the same as at inclusion. The targets initially defined in the inclusion assessment must be repeated as the endpoint defined as per RECIST v1.1.

- **Quality of life questionnaire**
  - EORTC QLQ – C30 (appendix 7 and 8)
    - **BEFORE** the 1st 6-week evaluation
    - **BEFORE** the 3rd 4-month evaluation

7.4 End-of-treatment assessment

This assessment **must be carried out 30 days** after discontinuing treatment

- **Clinical examination**
  - Clinical examination (including weight, BP)
  - ECOG performance index (appendix 2),
  - Assessment of tolerance as per CTC AE V4 criteria (appendix 5), Levi scale (appendix 4), and check for recovery from any toxicities at baseline or grade ≤ 1 (except alopecia)

- **Laboratory tests**

  - Blood electrolyte composition analysis (calcium, potassium, magnesium, sodium, bicarbonate, proteins, albumin)
  - Liver function (total and conjugated bilirubin, ALAT, ASAT, PAL, γGT, LDH),
  - Kidney function (creatinine clearance as per Cockcroft-Gault formula, creatininaemia, urea),
  - Full blood count and coagulation: FBC, platelets,
  - Tumour marker: ACE
  - Proteinuria (on urine strips) for arm A only

- **Quality of life questionnaire**
  - EORTC QLQ–C30 (appendix 7 and 8)

7.5 Post-progression assessment

After the end-of-treatment visit, follow-up shall be performed every 3 months until death or the end-of-study date (24 months after the inclusion of the last patient).

The starting point for follow-up is the date of the end-of-treatment assessment

- **Clinical examination**
  - Evaluation of survival (vital status).
  - List chemotherapy treatments prescribed after progression (3rd and 4th line)

The choice of subsequent treatment shall be left up to the investigator.

8. EARLY DISCONTINUATION OF TREATMENT

Patients are entitled to withdraw their consent and request to withdraw from the study at any time, regardless of the reason. The investigator is also entitled to withdraw a patient from the study early in the event of:

- toxicity,
- disease progression,
- pregnancy,
- refusal to continue the trial,
- withdrawal of consent,
- lost to follow-up,
- major breach of protocol,

Insofar as possible, patients who have discontinued their treatment early shall undergo follow-up under the same conditions as the other patients

9. TRIAL DISCONTINUATION CRITERIA

The trial may be temporarily or definitively terminated by the sponsor in consultation with the coordinator at the request of the Competent Authority and/or the Ethics Committee (EC), for the following reasons:

- unexpected frequency and/or severity of toxicity,
- insufficient patient enrolment,
- insufficient data collection quality:

10. EVALUATION CRITERIA

10.1 Primary endpoint

The primary endpoint is the evaluation of progression-free survival at 4 months of a cetuximab treatment versus bevacizumab each associated with fluoropyrimidine-based chemotherapy (CT) in a crossover regimen in wild-type RAS (KRAS and NRAS) progressive colorectal cancer patients after 1st-line chemotherapy associated with Bevacizumab.
Progression-free survival is defined as the time interval between the date or randomisation and the date of 1st local, regional, metastatic progression or death (regardless of cause) in the absence of progression. Living progression-free patients shall be censored at the date last seen.

10.2 Secondary endpoints

10.2.1 Efficacy

Objective tumour response rate (OR) defined as the occurrence of the Complete Response or Partial Response between the time of randomisation and the end of the treatment. An objective response is a complete response (CR) or partial response (PR). It shall be assessed every 6 weeks by CT scan or MRI as per RECIST v1.1 (2009).

Overall survival (OS) defined as the time interval between randomisation and death regardless of the cause, or the date last seen.

Overall survival from the date of the 1st-line chemotherapy of the metastatic disease. Defined as the time interval between the date of the 1st day of chemotherapy and death regardless of the cause, or the date last seen

10.2.2 Toxicity

Tolerance shall be assessed on the toxicity of the substances evaluated by clinical or biological means and rated according to the NCI CTCAE v4.0 scale (Appendix 5). For peripheral neuropathy, the modified Levi scale shall be used (Appendix 4).
The toxicity shall be evaluated at each visit (every 2 or 3 weeks), throughout the duration of the treatment.
To be assessable for toxicity, the patients must have received at least one cycle or administration of treatment.
The time to onset of grade 3-4 toxicity shall be studied and defined as the time interval between the date of first administration of the treatment and the date of first onset of grade 3-4 toxicity or the date of the last toxicity assessment in the absence of grade 3-4 toxicity.

Toxicity specific to bevacizumab and cetuximab as per CTCAE v4.0.

10.2.3 Quality of life

The quality of life under treatment, assessed using EORTC QLQ-C30 (Version 3, Appendix 8), shall be the combined primary endpoint.
A difference ≥ 5 points (longitudinal and/or transversal) is considered to be the smallest difference in a score having clinical significance.
The targeted dimensions are the overall health score, physical dimensions and fatigue.
The internal validation of this questionnaire, made up of 30 items, made it possible to identify 15 dimensions and calculate 15 scores:

- 5 functional aptitude scores (physical capacity, fitness to work or carry out any household task, cognitive capacity, emotional state, social status),
- an overall quality of life score,
- a financial problem score
- 8 symptom scores (fatigue, nausea/vomiting, pain, dyspnoea, sleep disruption, loss of appetite, constipation, diarrhoea).

The time to definitive deterioration of the overall health score is defined as the time interval between the date of randomisation and the date of a decrease in the quality of life score of more than 5 points without subsequent improvement by more than 5 points or the date last seen.

- Event: patient for whom a decrease in the score greater than or equal to 5 points with respect to the score at inclusion is observed, without subsequent improvement greater than or equal to 5 points or having missing date ("drop out").
- Censoring: patient for whom no decrease in the score greater than or equal to 5 points is observed or for whom a decrease of over 5 points is observed, but with subsequent improvement greater than or equal to more than 5 points.

10.2.4 Other endpoints

- Study the potential predictive factors for the response to anti-EGFR and anti-VEGF treatments (appendix No. 10)
- Evaluate CEC levels as predictive biomarkers of the efficacy of bevacizumab in association with chemotherapy for mCRC treatment (appendix No. 10)

11. DETERMINATION OF NUMBER OF PATIENTS AND STATISTICAL ANALYSIS

11.1 Number of subjects required

The primary objective of the study is the Progression-Free Survival (PFS). All patients should have at least 4 months of follow-up.

According to the Simon two-stage method (Optimax) with a 5% unilateral alpha error risk, a 90% power and the following hypotheses:

H0: A 30% Progression-Free Survival rate at 4 months is not of interest.
H1: A 50% Progression-Free Survival rate at 4 months is expected.

It is required to include 59 patients in each of the arms (total 118 patients).

At the end of stage 1, after the inclusion of 20 initial patients having at least 4 months of follow-up in each arm:

- If 6 or less than 6 living progression-free patients are observed after 4 months of follow-up (30.0%), the PFS rate being ≤ 30%, the treatment shall be deemed not to be of interest for the evaluation of this association of treatments and the inclusion for this arm shall be discontinued.
- If 7 or less more than 7 living progression-free patients are observed after 4 months, the inclusion for this arm shall be continued with 39 patients.

The power is 94%.

At the end of stage 2, after the inclusion of 59 patients having at least 4 months of follow-up in each arm:

- If 23 or less than 23 living progression-free patients are observed after 4 months of follow-up (39.0%), the PFS rate ≤ 30%, the treatment shall be deemed not to be of interest for the evaluation of this association of treatments.
- If 24 or more than 24 living progression-free patients are observed after 4 months of follow-up (40.7%), the PFS rate >30%, the treatment shall be deemed to be of interest for the evaluation of this association of treatments.

The power is 96% with an alpha error risk of 4.5%.

The total power is 90.2%, and the alpha error risk 4.5%.

In order to account for those lost to follow-up, 10% additional patients should be included.
A total of 132 patients shall therefore be included to obtain 118 patients suitable for analysis over an envisaged enrolment period of 5 years. The number of inclusions envisaged is approximately 3 patients/month. The patients included in this study cannot be included a second time. A patient withdrawn from the study, regardless of the reason, shall not be replaced.

During the analysis of the first stage, the inclusions shall not be stopped as the treatment administered is a standard in the care of this disease. Moreover, the trial steering committee shall monitor the toxicity of both treatment arms and may therefore request the independent review committee, if required, for an external opinion on the actions required.

11.2 Statistical analysis

No statistical comparison is envisaged between the arms in the randomised phase II study

The statistical analysis shall be conducted on an intention-to-treat basis. The intention-to-treat (ITT) population is defined as the set of included patients having received the complete study treatment or not.
The tolerance analysis population is defined as the set of included patients having received at least one administration of one of the study medicines.

The characteristics at inclusion of the total population (e.g. patients enrolled in the study) shall be described using descriptive statistics:

Frequency and percentage for categorical and ordinal variables,
Or
Mean (stable disease); median (Min-Max) for continuous and ordinal variables.

The PFS rate at 4 months, representing the percentage of the total population (ITT) with a 95% confidence interval (CI) in each arm, shall be analysed according to the Simon method. The number and type of progressions shall be reported in each arm.

The survival estimation shall be described with a median confidence interval (95%CI) with the Kaplan-Meier method.
The median follow-up shall be calculated according to the so-called "reverse Kaplan Meier" method for each of the arms with its 95% confidence interval
The theoretical follow-up period estimation shall be the time interval between the date of inclusion and that on which the database is frozen.

The time-related parameters (PFS, OS) as well as the time to definitive deterioration of a quality of life score (scores) shall be estimated according to the Kaplan-Meier method and described with a median confidence interval (95%CI) and rates at defined periods.
Patients free from specific events at the end of the study (freezing of the study database) shall be censored, for the "Time" endpoint, at the date last seen.

Quality of life

A 5% deviations shall be defined as the minimum clinically significant difference/value.
Missing QoL data shall be analysed by calculating the rate of QLQ-C30 questionnaire completion during follow-up (observed/expected). The non-random inclusion of missing questionnaires shall also be calculated for this rate, based on the discontinuation of treatment and progression at each follow-up visit.
- The following shall be reported: The rate of patients showing an improvement in the QLQ-C30 score (any positive change and any change greater than 5 points), or stabilisation between the time of inclusion and the last follow-up, with respect to all eligible patients at inclusion and with respect to patients for whom the scores are available.
The time to definitive deterioration of the general health, physical function and fatigue scores.
- In order to study the progression over time of the quality of life scores, combined analysis of variance models for repeated measurements of each of the scores in each of the arms shall be applied.

Adverse events shall be compiled at each visit and assessed according to NCIC-CTC version V4.
The following parameters shall be reported:
- Number and percentage of patients presenting with at least one AE.
- Number and percentage of patients presenting with at least one grade 3-4 AE.
- Number and percentage of patients presenting with at least one SAE.
- Number and percentage of patients presenting with at least one study treatment-induced AE and one grade 3-4 AE.
- Number and percentage of patients presenting with at least one AE leading to discontinuation of the treatment.
The relationship with the study, results, severity, grade, dose adjustment and other specific AE-related actions shall be reported in the Case Report Form.

An estimation of the time to onset of grade 3-4 toxicity shall be carried out using the Kaplan-Meier method.
The data shall be analysed with Stata software (V10).

12. ETUDES ANNEXES

Cf. Annexe n°9 et procédures du classeur investigateur

13. SERIOUS ADVERSE EVENT

13.1 General definition

An adverse event (AE) is defined as any untoward medical occurrence, in a patient or clinical trial subject treated by a medicinal product and which does not necessarily have a causal relationship with this treatment.

A serious adverse event (SAE) is defined as any event:

- results in death,
- is life-threatening,
- requires hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly or birth defect,
- or is medically relevant in the context of the pathology and the clinical trial.

The following are considered as medically significant: all clinical events or laboratory results considered as serious by the investigator and that do not correspond to the criteria defined below. They may place the patient at risk and require medical intervention to prevent an issue that corresponds to one of the seriousness criteria previously mentioned (e.g., overdose, second cancers, pregnancy, and new events may be considered as medically significant).

The terms invalidity and incapacity corresponds to all temporary or permanent physical or psychiatric handicaps, clinically significant and affecting the patients physical activity and/or quality of life.

The following are not considered as serious adverse events (SAE):

- A hospitalisation for <24 hours.
- A hospitalisation programmed prior to the patients inclusion in the study and/or planned for the protocol (biopsies, chemotherapy).
- Disease progressions are not to be declared as SAEs.
- All biological anomalies of grade 3 or 4 not resulting in any clinical complication that correspond to the seriousness criteria already described, will not be reported as SAEs.

13.2 Definition of expected serious adverse event (expected-SAE)

An expected-SAE is an event already mentioned in the latest version of the investigator brochure (IB) or summary of product characteristics (SmPC). An expected-SAE is an event already mentioned in the most recent version of the IB or SmPC for molecules that already have marketing authorisation. The same definition applies to drugs/medications administered during a clinical study in the same population but not within the marketing authorisation indication.

13.3 Definition of an serious unexpected serious adverse reaction (unexpected-SAE/SUSAR)

An unexpected-SAE/SUSAR is any event that is not mentioned or is different in nature, intensity, or evolution compared to those mentioned in the IB or SmPC for products/medications that have marketing authorisation.

13.4 Severity criterion

The severity criterion must not be confused with the seriousness criterion which is the guide for defining the reporting requirements.
The intensity (severity) of events will be estimated using the extract of CTCAE v4.0 classification (see appendix 4 and 5). 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 normal everyday activity of the patient
Moderate (grade 2): perturbs the normal everyday activity of the patient
Severe (grade 3): prevents the normal everyday activity of the patient
Very severe (grade 4): requires urgent intervention/life threatening
Death (grade 5)

13.5 Procedure to follow if a serious adverse event occurs

The investigator must inform the pharmacovigilance at R&D UNICANCER (PV-R&D UNICANCER) of all **Serious Adverse Events expected (expected-SAE) and unexpected (unexpected-SAE/SUSAR),** whether or not related to the research, that occurs from the signing of the consent document and throughout the study and up until 30 days after the last treatment administration.

All late SAEs considered as reasonably related to a study treatment or to the research must be declared. There is no delay limit for the reporting of these related events.

The declaration of SAEs for a given patients begins at the date of signing of the consent document, sent by fax, as soon as the investigator becomes aware of the event, to the PV–R&D UNICANCER,

R&D UNICANCER
Pharmacovigilance
Tel: 01 44 23 04 16 – Fax: 01 44 23 55 70
email: pv-rd@unicancer.fr

of the notification of a new SAE form that can be found in the investigator file.

The investigator must note, among other details, the following for each event:

- A description of the event as clearly as possible using medical terminology,
- The intensity,
- The start and end date of the event,
- The measures taken and whether or not corrective treatment was required,
- If the study treatment was delayed,
- The evolution of the event. In the case of non-fatal events, the evolution should be followed until cure or resolution of the event to the same state as prior to the event, or until stabilisation of eventual sequela,
- The causal relation between the event and the study treatment or related to study (period without treatment, complementary examinations required during the study etc.),
- The causal relation with the disease/pathology being treated, or another disease/pathology, or another treatment.
- The investigator must also attached to declaration of SAE, with every declaration if possible (if applicable):
  - A copy of hospitalisation or the prolongation of hospitalisation report,
  - A copy of the autopsy report,
  - A copy of all the complimentary examination results, including pertinent negative results, with the corresponding laboratory normal values,
  - All other documents considered useful and pertinent.

All these documents must be anonymised.
Complimentary information may be requested (by fax, telephone or during a site visit) by a clinical research associate and/or a member of the pharmacovigilance - R&D UNICANCER using a data clarification form (DCF).

Nonetheless, all events expected but different by their intensity, evolution, or frequency will be considered as unexpected by the pharmacovigilance.

13.6 SAE follow-up

*The investigator is responsible for the appropriate medical follow-up of the patient until resolution or stabilization of the event or until the patient dies. **Under certain cases, this may imply that the follow up may continue after the withdrawal of the patient from the study.**

Complimentary information must be transmitted, as soon as available, to the PV-R&D UNICANCER using the SAE declaration form (by checking the «Follow up report N°» case to show that the declaration is a follow-up report and not an initial declaration. The investigator must also provide the final report, declaring the last follow up at resolution or stabilization of the SAE.

The investigator must conserve all the documents concerning the SAE in order to allow, if necessary, to complete the information already declared.
The investigator must respond to all requests for complimentary information from the PV-R&D UNICANCER to be able to completely document the event.

13.7 Pregnancy

In case of pregnancy, this should be reported to the pharmacovigilance R&D Unicancer using the Pregnancy Notification Form in the investigator file, within 7 days:

R&D UNICANCER
Pharmacovigilance
Tel: 01 44 23 04 16 – Fax: 01 44 23 55 70
email : pv-rd@unicancer.fr

14 QUALITY CONTROL AND QUALITY ASSURANCE

The sponsor is responsible for implementing a quality assurance system described in federal procedures, so that the trial is conducted in accordance with the protocol and GCP.

14.1 Monitoring committees and Steering Committee:

A trial Steering Committee made up of the study coordinator, sponsor project manager and trial statistician (COPIL = Study Steering Committee) shall be set up to guarantee patient protection, ensure that the trial is conducted in an ethical manner, assess the benefit/risk ratio of the trial and review the scientific results during and at the end of the trial.

An Independent Data Monitoring Committee (IDMC) shall be formed to analyse the results of various stages of the study.

14.2 Quality assurance

14.2.1 Data collection

Consignement of all data necessary to the research must be stated in the trial case report forms (CRFs). CRFs will be completed by the clinical investigator or another designated member from his/her staff.
Inputs in CRFs must be made with a ballpoint pen (not a pencil) and must be clearly legible. Correction pen or fluid can not be used.
Necessary corrections will be made by the investigator or a designated member of his/her staff as follows: the erroneous data must be crossed out but should remain legible, and the correct input written nearby, dated and signed, by the person correcting it.

The original of the information booklet and informed consent is kept in the investigator file.

The following data will be collected in the CRF completed by the investigator or a designated member :

- Clinical examination, weight, height, vital signs
- Blood and biological test
- Tumor evaluations according to RECIST criteria,
- Adverse events and serious adverse events occurring at each cycle
- Etc.…

14.2.2 Research Monitoring

To ensure data authenticity in accordance with the Good Clinical Practices (BPC of November 24, 2006), the sponsor establishes a system of quality assurance that consists of:

- managing the trial monitoring according to the UNICANCER procedure,
- data quality control (for all data from participating centers) by the CRA with:
  - verifying that the protocol, as well as the Good Clinical Practices, the laws and regulations currently in force are accurately followed,
  - verifying the consentement and eligibility of each patient participating in the research,
  - verifying the CRF data are consistent and in agreement with the source documents,
  - verifying the notification of each SAE,
  - verifying the drug traceability (dispatching, stockage and accounting),
  - verifying, if applicable, that patients are not already participating in another research study which may exclude their inclusion in the research offered by the protocol. The sponsor also ensures that patients have not taken part in research for which an exclusion period is currently required.
- auditing the participating centers when deemed necessary
- the centralized review of the objective response

The experts in charge of research monitoring will be mandated by the sponsor. They must have access to all patient data as is necessary to their mission and are bound by professional secrecy under the regulation of the French penal code (articles 226-13 and 226-1). Written reports must be issued to ensure monitoring traceability.
The clinical investigators will commit to giving the monitoring experts and the representatives of the competent authorities direct access to all patient files.

15. DATA OWNERSHIP AND CONFIDENTIALITY MANAGEMENT

Until the trial results are published, the investigator is responsible for insuring the confidentiality of the totality of the information, handled by herself/himself and all other individuals involved in the course of the trial, supplied by UNICANCER. This obligation holds for the information that the investigator may communicate to the patients within the context of the trial and for any already published information as well.

The investigator commits not to publish, not to spread or use in any manner, directly or indirectly, the scientific and technical information related to the trial.

Nevertheless, in conformity with the article R 5121-13 of the Public Health Code, both the center and the investigator may communicate information relative to the trial:

- to the Health Minister,
- to the public health inspectors who are doctors,
- to the public health inspectors who are pharmacists,

- to the AFSSAPS/ANSM General Director and inspectors.

The trial will not be the subject of any written note and/or oral comment without the prior agreement of the sponsor; the totality of the information that is communicated or obtained during the course of the trial belongs in full right to the Unicancer that can freely use it.

16. PUBLICATION RULES

Publishing PRODIGE trials within a reasonable time in peer-reviewed scientific journals with wide audience (good impact factors) is one essential objective for therapeutic progress. The Coordination Committee of PRODIGE (CCP) is responsible for ensuring that this objective is reached and will decide:

- when the preliminary and the final results of the study should be published.
- who are the members of the writing committee (maximum 5 members).

All information resulting from this trial is considered to be confidential, at least until appropriate analysis and checking has been completed by the sponsor, the principal investigator and the statistician of the trial.

The Coordination Commitee may delegate its responsabilities to the principal investigator.

In any case, the CCP validates the choices that have been made by the writing committee regarding publishing and ensures that delays are respected. The absence of response from the CCP within a delay of one month implies acceptance.

1) The writing committee includes

- The principal investigator (and the associate principal investigator, if applicable) who has written the initial protocol. The principal investigator will be first author unless exceptionally decided otherwise.
- The statistician(s) who have performed the design and statistical data analysis;
- The most important contributors;
- Possibly, an expert who has contributed in an exceptional way to the data analysis (biologist, anatomopathologist,…).
-

2) The first author commits to produce a manuscript ready for publication within a delay determined by the CCP. The delay should not exceed one year after the end of the trial. In case the first author is in the impossibity to comply with this obligation another first author will be designated by the CPP. To help writing the articles related to the trials, the service of a medical writer may be used and working meetings organized in collaboration with the first author and the statistician(s).

Before any article is published, the list of patient inclusions per center and the list of clinical investigators participating in the trial will be made available to the all other investigators of the trial.

3) Order of authors: it will be determined according to their contribution and the number of patients included::

- The first author
- The members of the writing committee (as defined previously)
- A limited number of investigators, 1 per center, listed in decreasing order of importance (number of patients included). In some particular cases, the trial's steering committee may decide that 2 investigators from the same center are both authors. These criteria will be weighed to allow small centers with dedicated inclusion effort to be represented in the list of authors. The CCP will validate this process so that everyone's interests are

preserved.

- The maximum number of authors authorized by the journal targeted for submission will be used.
- Irrespective of the number of included patients, there will be at least one author representing FFCD or UNICANCER.In articles reporting sub-studies, authors may differ from those of the princeps article and reflects the scientific specialty involved; e.g.: in radiochemotherapy (RCT) trials an article dedicated to radiotherapy may be signed by radiotherapists who are participating as co-investigators. The first author of the princeps article will be last last author in substudy publications (possibly refered to as “having equally contributed”).
- The Prodige partnership must appear in the title or after the author list. In the case of cooperative trials, the first partnership quoted is the one that has initiated the trial. Other collaborative associations/partnerships are mentioned in order of their importance under the condition that they have included at least 5% of patients..
- Usually the statistician appears after the third position in the author list. However, he/she may be first or second author in specific articles.

All the participants who do not appear in the author list are cited at the end of the article. The data manager is also cited or may appear in the author list if the CCP deems it justified.
Partners are acknowledged.
Before it is submittted to a journal, the authors and the sponsor will receive a copy of the manuscript. They commit to reading and sending it back with their written comments and criticisms within 15 working days (30 days during the summer semester).

4) Oral communications:

With a prior agreement from the CCP or the Steering Committee, an investigator may present orally on her/his behalf all or part of the results. The rules for citing authors are generally the same for oral presentations as for the published articles. However, the order of authors may differ between articles and oral communications and according to the congress wherein the research is presented. In some particular cases (e.g.: multidisciplinary, pathological, biological, echo-endoscopic studies conducted in parallel with the therapeutic trial) other authors may be selected. The PRODIGE partnership and other associations, if any, must be quoted as well.

17. ETHICAL AND REGULATORY ISSUES

Les patients inclus dans cette étude ne pourront pas participer simultanément à une autre recherche et une période d’exclusion à l’issue de la recherche est de 30 jours.

The clinical trial must be conducted in accordance with:

- the principles of ethics as stated in the last version in use of the Declaration of Helsinki,
- the Good Clinical Practices of November 24th, 2006,
- the European directive 2001/20/CE on the conduct of clinical trials,
- the Huriet’s law (n° 88-1138) of December 20th, 1988, relative to the protection of persons participating in biomedical research and modified by the Public Health Law n°2004-806 of August 9th , 2004,
- the law on ‘digital information and Freedom’ (Informatique et Libertés n° 78-17) of January 6th,1978 modified by the law n° 2004-801 of August 6th, 2004 relative to the protection of persons with regard to the computerized processing of personal data,
- the bioethics law n° 2004-200 of August 6th, 2004.

17.1 Authorization for the clinical trial

The protocol has been submitted to, and approved by, the "Ouest III" Ethics Committee.
The protocol has been submitted to, and approved by, ANSM.

17.2 Information and consent of the participants

Prior to carrying out biomedical research on human subjects, a free and written informed consent form must be signed by each individual participating in the trial after she/he has been informed by the investigator during a physician-patient consultation and after sufficient time for reflection has been allowed.

The information booklet and informed consent form (must be associated within the same document to insure that the whole information is given to the research participant.

The consent form must be dated and signed by both the participant in research and the investigator. All pages of the information booklet must be signed by the participant. The original document is archived by the investigator; a copy will be returned to the research participant.

In the case the objective of the trial is to carry out genomic or proteomic analysis, the information booklet must specify the type of research that will be undertaken and the patient must be given the right to accept or refuse that the biological samples taken from her/him be kept for the purpose of conducting scientific research.

Within the scope of this biomedical research, personal data shall be processed in order to facilitate analysis of the clinical trial results with regards to the objective thereof.
To this end, medical data pertaining to the patient and data pertaining to his/her lifestyle shall be forwarded to the Sponsor. These data shall be identified by a code number and by the first three letters of the patient's name. These data may also be transmitted to French or foreign Health Authorities under conditions ensuring their confidentiality. In accordance with the French data protection law, the patient is entitled to access and rectify his/her personal data. He/she is also entitled to oppose the forwarding of data covered by professional confidentiality liable to be used within the scope of this trial and to be processed.
He/she may also access all of his/her medical data directly or via a doctor of his/her choice by applying the provisions of Article L 1111-7 of the French Public Health Code.
These rights are exercised with the doctor responsible for follow-up within the scope of the trial, who knows his/her identity.

17.3 Responsabilities of the sponsor

The sponsor of the trial, UNICANCER, is the moral person who: takes the initiative of conducting biomedical research on human subjects, and is therefore accountable for the research management and for verifying that the financing schedule covers the anticipated expenses.

The main sponsor responsibilities are:

- to subscribe a civil-responsibility insurance,
- to obtain an EudraCT (European Drug Regulatory Authorities Clinical Trials) identification number,
- to register the trial in the European data base,
- to request the opinion of the Committee for the Protection of Patients (CPP) “Ouest III “ and ANSM on the initial project and the substantial amendments; advice from the CPP and approval from ANSM.

- to provide information on the trial to the heads of the health care centers, the appropriate investigators and the pharmacists,
- to declare to the competent authorities, i.e. the ANSM and the EMEA (the European pharmacovigilance data bank, Eudravigilance) any suspicion of unexpected serious adverse events (U-SAE) related to any of the treatments used in the trial and communicate the information to the CPP and the investigators of the trial,
- to file annually the security report to the competent authority and the CPP "Ouest III",
- to declare the beginning and end of the trial to the competent authority,
- to edit the final report on the trial, and communication to ANSM
- to communicate the information on the trial's results to the competent authority, the CPP "Ouest III" and the research participants,
- to archive the trial's essential documents in the sponsor folder for a minimal duration of 15 years after the research is ended.

17.4 Responsabilities of the clinical investigators

The main investigator of each health care center participating in the study commits to conducting the clinical trial in compliance with the study protocol that has been approved by the CPP "Ouest III" and the competent authority (ANSM).

The investigator must not make any modification to the protocol without having obtained written authorization of the sponsor and the proposed modifications have been authorized by the CPP "Ouest III" and the competent authority.

It is the responsibility of the main investigator:

- to provide the sponsor with its own curriculum vitae and co-investigators' curriculum vitas,
- to identify the members of its team who participate in the trial and to define their responsibilities,
- to start recruiting patients after the sponsor has issued its authorization.
- To be available for the monitoring visit and for investigators meeting.

It is the responsibility of each investigator:

- to observe confidentiality concerning the trial,
- to collect the informed consent form, dated and signed personally by each individual research participant before any selection procedure specific to the trial may start,
- to regularly fill in the observation handbook (CRF) for each patient included in the trial and allow the clinical research assistant (CRA) mandated by the sponsor to have direct access to the source-documents in order to validate the data collected in the observation handbook.
- to report to the Sponsor, without delay, any serious adverse event occurring in the course of the trial,
- to accept regular visits of the study monitor and possibly the auditors as mandated by the sponsor or the inspectors of the competent legal authorities.
- to date, correct and sign the corrections made in the observation handbook for each patient included in the trial,

17.5 Regulations relating to the collection of human biological samples

Within the scope of the translational research of this study (see section and appendix 9), tumour samples are required both for anatomopathological tests and genetic tests; these are subject to specific written consent from the patient. This consent, which is different to the consent to take part in the clinical trial, may be withdrawn at any time. Similarly, at any stage of the trial, the patient has the option of requesting the destruction of his/her samples.

At the end of the trial, without opposition from the patients and if these samples have not been fully used, they may be the subject of subsequent scientific research solely on the sponsor's approval. In the case of subsequent genetic research, in accordance with the French bioethics law, patients shall be again requested for their consent.

Within the scope of translational research, personal data shall also be processed in order to enable analysis of the biological research results.
To this end, biological data, including genetic data, shall be associated with certain medical data from the clinical trial and shall be forwarded to the Sponsor. The data shall be identified by a code number and/or by initials. These data may also be transmitted to French Health Authorities under conditions ensuring their confidentiality. In accordance with the French data protection law, the patient is entitled to access and rectify his/her personal data. He/she is also entitled to oppose the forwarding of data covered by professional confidentiality liable to be used within the scope of this trial and to be processed.
He/she may also access all of his/her biological and medical data directly or via a doctor of his/her choice by applying the provisions of Article L 1111-7 of the French Public Health Code.
These rights are exercised with the doctor responsible for follow-up within the scope of the trial, who knows his/her identity.

17.6 Federation of the Patients Committee for Clinical Cancer Research

The patient committees' federation is coordinated by the R&D UNICANCER .It includes both the patient committees of the LNCC and from other health care centers. It commits to: rereading the protocol and proposing improvements dealing principally with the quality of the letter of information to the patients, the setting up of a treatment and monitoring plan, and suggesting measures aimed at ameliorating the comfort of the patients.

18. RESEARCH DATA PROCESSING AND DOCUMENT ARCHIVING

18.1 Data processing

Statistical data analysis will be transferred to the Biostatistical Unit of the ICM under the responsability of Sophie Gourgou-Bourgade. All data from the trial remain the property of UNICANCER, the research sponsor.
The software Clinsight® will be used for data input, management and archiving.
Statistical analysis will be performed using the Stata v10.0.software.

Data processing (input + data management) will be transfered by UNICANCER to the Biostatistical and Epidemiological Unit of Centre Georges-François Leclerc under the responsability of Franck Bonnetain. The software Capture system will be used.
The corresponding database is declared to the CNIL by the biostatistical unit. All data from the trial remain the property of UNICANCER, the research sponsor.

Data shall be processed in according to the appended guiding principles for computer systems in the European Community Good Clinical Practice Guidance document

In accordance with the revision of the law ''loi informatique et liberté'' of August 6th, 2004 and its application decree, UNICANCER commits to complying with the reference MR001 methodology establish by the Commission Nationale de l'Informatique et des Libertés (French national commission on digital information and freedom).

18.2 Document archiving

All documents regarding the study (protocol, consent forms, observation handbook, investigator's files, etc.) as well the original documents (laboratory results, radiographies, patient records, clinical examination reports, etc.) must be kept in a locked and secured place and considered to be confidential material.

Data will be archived under the responsibility of the main investigator of each participating center according to the regulation in force (order of November 8, 2006). The archives will be kept as well as a list of patient identifications for a minimum period of 15 years after the end of the study. After this delay, the site can destroy the documentation after written approval from the sponsor.

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Appendix 1 – Treatment and examination schedule

Visits	Baseline visit	Evaluation during treatment period and until progressive disease							Evaluation of the tumor	Evaluation after treatment	Evaluation after progression
		C1	C2	C3	C4	C5	…..	Cn	Every 6 weeks and until progression	D30 After the end of treatment	Every 3 months and for a maximum of 2 years
Criteria/ Informed Consent/randomisation	X	Treatment will be administered every two weeks depending on the chemotherapy et until progressive disease							To be done before the next cycle		
TREATMENTS											
Chemotherapt + cetuximab or bevacizumab		X	X	X	X	X		X			
CLINICAL EVALUATION											
Histoire de la maladie et Antécédent	X										
Poids /taille / signes vitaux TA / ECOG	X	X	X	X	X	X		X		X	
ECG	X										
Toxicity and tolerance		X	X	X	X	X		X		X	
Vital status and post progression treatment										X	X
QLQ- C 30[(1)] to be done before evaluation	X	X							X 1st et 3rd éval	X	
EVALUATION OF THE TUMOR *											
thoracic-abdominal-pelvic CT scan * [(2)]	X								X		
BIOLOGICAL EVALUATION											
Hematology and coagulation	X	X	X	X	X	X		X		X	
Blood ionogram	X	X	X	X	X	X		X		X	
Hepatic evaluation	X	X	X	X	X	X		X		X	
Renal evauation	X	X	X	X	X	X		X		X	
Urine test (bandelettes urinaire) arm A	X	X	X	X	X	X		X		X	
Tumor biomarker: CEA	X	X	X	X	X	X		X	X		
Pregnancy Test	X										
TRANSLATIONAL RESEARCH Appendix 9 et 10											
Tumor bloc	X										
Blood samples (3ml)	X										

(1) QLQ to be done before randomisation / before cycle 1 / before 1st evaluation / before evaluation at 4 months / and at the end of treatment visit.
(2) Brain scan in the event of suspected brain metastases and bone scan in the event of suspected bone metastases

*The same exams shall be done at baseline visit and during all the study. At baseline, the exams shall be done within 28 days before randomization.

APPENDIX 2

Performance status evaluation – WHO scale

Performance status ECOG-ZUBROD/ WHO	ECHELLE
Fully active, able to carry on all pre-disease performance without restriction.	0
Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work.	1
Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours	2
Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	3
Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	4

Appendix 3 – Classification for tumor evaluation RECIST V1.1 (version V1.1 2009)

"New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1)" E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J. Verweij ; Eur J Cancer, 4 5 (2 0 0 9) 2 2 8 -–2 4 7.

RECIST 1.1 Guidelines

	RECIST 1.0	RECIST 1.1	Rationale for Change
Measurable Tumor Burden	A maximum of 10 target lesions in total (and up to 5 per organ) can be identified at baseline and measured through the course of therapy.	A maximum of 5 target lesions in total (and up to 2 per organ) can be identified at baseline and measured through the course of therapy.	Data warehouse analyses showed no loss of information when the maximum measurable lesion count was reduced from 10 to 5. A maximum of 2 lesions per organ yields sufficient representation per disease site.
Minimum Size of Measurable Lesions	• ≥10 mm in longest diameter (LD) for spiral CT (nodal & extranodal lesions) • ≥ 20 mm in LD for non-spiral CT • ≥ 20 mm in LD for clinical lesions • ≥ 20 mm in LD for chest x-ray (if clearly defined & surrounded by aerated lung); CT is preferable • Ultrasound (US) may be an alternative to clinical measurement of superficial palpable nodes, subcutaneous lesions & thyroid nodules	• ≥ 10 mm in LD and 2X the slice thickness for extranodal lesions • ≥ 15 mm in short axis diameter (SAD) for nodal lesions • ≥ 10 mm in LD for clinical lesions (must be measured using electronic calipers) • ≥ 20 mm in LD for chest x-ray (if clearly defined & surrounded by aerated lung); CT is preferable • US cannot be used to measure lesions	Additional guidance was necessary for CT scans with a slice thickness of > 5 mm. Lymph nodes are normal anatomic structures. The SAD of lymph nodes is more predictive of malignancy than the long axis. US exams cannot be reproduced in their entirety for independent review and since they are operator-dependent, it cannot be guaranteed the same technique & measurements will be made at all assessments.
Lymph Nodes	Nodal lesions not distinguished from extranodal lesions The sum of the longest diameters of target lesions followed through the course of therapy	Lymph nodes are considered pathologically enlarged if > 10 mm in SAD. To be measurable, nodal lesions must be ≥ 15 mm in SAD. Nodal lesions with SAD > 10 mm and < 15 mm are non-measurable. The sum of the diameters (LD for extranodal target lesions, SAD for nodal lesions) is followed through the course of therapy.	It was necessary to define pathological enlargement of lymph nodes. The SAD of lymph nodes is more predictive of malignancy than the long axis.
Bone Lesions	Bone lesions are non-measurable.	A lytic or mixed lytic-blastic bone lesion with a soft tissue component assessed on CT/MRI can be measurable if the minimum size criteria are met. Blastic bone lesions & bone lesions assessed on bone scan, PET, or plain films are non-measurable.	Certain bone lesions can be measured and at times, it may be appropriate to include them in the baseline target disease.
Cystic Lesions	Cystic lesions are non-measurable.	Lesions that meet the criteria for radiographically defined simple cysts are not malignant. Cystic lesions thought to be metastases can be measurable if they meet the minimum size criteria. Non-cystic lesions are preferable.	Certain cystic lesions can be measured and at times, it may be appropriate to include them in the baseline target disease.
Lesions with Prior Local Treatment	Lesions in previously irradiated areas may or may not be considered measurable (conditions should be defined in study protocols).	Lesions in previously irradiated areas (or areas treated with local therapy) are not measurable unless the lesion has progressed since therapy. Conditions should be defined in study protocols.	Some lesions that have progressed since local therapy can be measured and it may be appropriate to include them in the baseline target disease.
Too Small To Measure	Not discussed	If a target lesion becomes too small to measure, a default value of 5 mm is assigned. If the lesion disappears, the measurement is recorded as 0 mm.	Measurement of small lesions is not reproducible. Providing a default value prevents assessments based upon measurement error.

RECIST 1.1 Guidelines

	RECIST 1.0	RECIST 1.1	Rationale for Change
Lesions which Split or Coalesce	Not discussed	If extranodal target lesions fragment, the LDs of the fragmented portions are added to the sum. If target lesions coalesce and cannot be distinguished, the LD of the coalesced lesion is added to the sum.	Use cases which were not defined in RECIST 1.0
Definition of Complete Response (CR)	CR requires the disappearance of all lesions and the normalization of tumor marker level.	CR requires the disappearance of all extranodal lesions, the regression of all nodal lesions to < 10 mm SAD & the normalization of tumor marker level.	Lymph nodes are normal anatomic structures and are no longer considered pathologically enlarged if the SAD regresses to < 10 mm.
Definition of Progressive Disease (PD)	PD is assessed if the sum of the longest diameters increases by ≥ 20% from nadir (smallest sum on treatment). PD is assessed if there is "unequivocal progression" of existing non-target lesions.	PD is assessed if the sum of the diameters has increased by ≥ 20% and ≥ 5 mm from nadir (including baseline if it is the smallest sum). Patients with measurable disease: for "unequivocal progression" based on non-target disease, there must be an overall level of substantial worsening that merits discontinuation of therapy (if target disease is SD/PR). Patients without measurable disease: for "unequivocal progression" of non-target disease, the increase in overall tumor burden must be comparable to the increase required for PD of measurable disease.	Clarification that if baseline is the smallest sum, it is the reference against which PD is assessed. The PD requirement of a ≥ 5 mm increase guards against PD when the total sum is small and a 20% increase is within measurement error. There was confusion with RECIST 1.0 as some were assessing PD based on an increase in any non-target lesion even when the target disease was stable or responding.
Assessment of New Lesions	Not specifically defined	New lesions should be unequivocal and not attributable to differences in scanning technique or findings which may not be tumor (i.e. 'new' bone lesions may be healing or flare of pre-existing lesions). If a new lesion is equivocal, repeat scans are needed to confirm. If confirmed, PD is assessed at the date of the initial scan. Lesions identified in anatomic locations not scanned at baseline are considered new. New lesions on US should be confirmed on CT/MRI.	The appearance of new malignant lesions results in PD; therefore additional guidance regarding the detection of new lesions is important.
FDG-PET	No specific recommendations	New lesions can be assessed using FDG-PET: (-) PET at baseline and (+) PET at follow-up is PD based on a new lesion No PET at baseline and (+) PET at follow-up is PD if the new lesion is confirmed on CT. If a subsequent CT confirms the new lesion, the date of PD is the date of the initial PET scan. No PET at baseline and (+) PET at follow-up corresponding to a pre-existing lesion on CT that is not progressing: not PD	While RECIST 1.1 is not yet incorporating FDG-PET into the response assessment, it is reasonable to use PET to complement CT scanning in the assessment of PD (particularly for the identification of new disease).
Recurrence of Lesions	Not discussed	For a patient with SD/PR, a lesion which disappears & then reappears will continue to be measured and added to the sum. Response will depend upon the status of the other lesions. For a patient with CR, reappearance of a lesion would be considered PD.	Most lesions have not disappeared but are not visualized because they are beyond the resolving power of the imaging modality employed.
Overall Response	Overall response table integrates target, non-target & new lesions	One overall response table integrates target, non-target & new lesions and another table integrates non-target & new lesions for the assessment of subjects without measurable disease.	RECIST is being used in trials where PFS is the primary endpoint and not all patients have measurable disease at baseline.
Confirmation of Response	CR and PR require confirmation by a repeat assessment no earlier than 4 weeks after the criteria for response is first met.	Confirmation of PR/CR is ONLY required for non-randomized trials where response is the primary endpoint. In these trials, subsequent confirmation of PR with one interim time point of SD is acceptable.	Data warehouse analyses showed response rates rise when confirmation is eliminated, however the only circumstance where this is important is in trials with no concurrent comparative control & where response is the primary endpoint.

Appendix 4 – Neurotoxicity: Levi scale

Toxicities	Grade 0	Grade 1	Grade 2	Grade 3
Symptoms	None	Paraesthesia / dysaesthesia to cold, of brief duration with full recovery at the start of the next cycle	Paraesthesia / dysaesthesia to cold of prolonged duration, persisting at the start of the next cycle Permanent discomfort perceived by the patient as not affecting normal activities	Paraesthesia interfering with day-to-day life. pain, discomfort when walking, writing, etc.

Ref: Levi F, et al. Oxaliplatin activity against metastatic colorectal cancer. Eur J Cancer; 1993;29:1280-4

Appendix 5 – Toxicity Criteria (CTCAE)

Please refer to the Common Terminology Criteria for Adverse Events (CTCAE), separately joined to this protocol or available on :

http://ctep.cancer.gov/

Common Terminology Criteria for Adverse Events v4.0 (CTCAE)
(Publish Date May 28, 2009)

Annexe 6 – Summary of the Products Characteristic

The SmPC of bevacizumab and cetuximab are available in the investigator file.

Please refer to the current version on ANSM, EMEA or VIDAL websites.

http://agmed.sante.gouv.fr/
http://www.emea.eu.int/
http://www.vidalpro.net/

Annexe 7 – Conseils pour l'utilisation du questionnaire EORTC QLQ-30 pour mesurer la qualité de vie

1 – PASSATION DU QUESTIONNAIRE

- Fournir un environnement calme et confortable pour le remplissage du questionnaire.
- Remettre le questionnaire au malade en personne en pensant à emporter un stylo bille supplémentaire (le patient peut ne pas avoir de stylo avec lui).
- Prévoir une aide par une personne désignée (par exemple infirmière, assistante, technicienne de recherche clinique, secrétaire) au cas où le malade ait besoin d'explications.
- Expliquer verbalement les instructions ou les questions si celles-ci ne paraissent pas claires sans influencer les réponses. Lui montrer comment entourer (et non cocher) les réponses.
- Parfois remplir à la place du patient en lui posant les questions (patients âgés, fatigués ou ayant oublié ses lunettes …) et alors le mentionner.
- Vérifier lors de la récupération du questionnaire que les données non remplies le sont délibérément et ne résultent pas d'un oubli.
- Noter la cause du refus si le patient refuse de remplir l'ensemble du questionnaire.

2 – MOMENT DE REMISE DU QUESTIONNAIRE

a – Avant l'inclusion

- Le patient doit être au courant de sa situation avant le remplissage du questionnaire de qualité de vie.
- Le médecin doit avoir expliqué le but du questionnaire.
- Faire remplir le questionnaire avant randomisation pour que l'issue de la randomisation n'influe pas les résultats de qualité de vie.
- Le remplissage du questionnaire sera un critère d'inclusion, car disposer du questionnaire avant traitement permettra de détecter un biais de sélection si le suivi ultérieur vient à manquer (patients avec une qualité de vie médiocre à l'inclusion auxquels on n'ose plus ensuite présenter un questionnaire car la QdV s'est encore dégradée).

b – Avant chaque cure

- Le questionnaire est considéré comme acceptable s'il est rempli le jour du traitement ou dans les 3 jours qui précèdent celui-ci. Le remplissage par téléphone est déconseillé.
- Si le traitement est reporté, le remplissage du questionnaire le sera également.

c – A chaque remise de questionnaire

- Le questionnaire est remis au malade et rempli préférentiellement avant que celui-ci ait vu le médecin, à la fois pour réduire les biais liés au dialogue avec le médecin ou ceux dus aux résultats du traitement et aussi pour permettre au patient de discuter avec le médecin des symptômes ou des domaines de qualité de vie réduite.
- Déconseiller d'emmener le questionnaire à la maison car il n'y aura aucun contrôle sur le jour où le questionnaire sera rempli réellement et les réponses au questionnaire seront influencées par la famille ou les amis.
- En cas de symptômes sévères décrits sur le questionnaire de qualité de vie, la personne qui récupère le questionnaire peut rappeler au patient qu'il doit signaler les problèmes au médecin responsable de sa chimiothérapie.
- Il faut remettre le questionnaire à chaque cure prévue et aussi à la sortie d'étude, même si le patient ne va pas bien (c'est précisément à ce moment-là qu'il est intéressant d'étudier les altérations de la qualité de vie et qu'il est important de tenter de les corriger).

3 – ORGANISATION INTERNE DE CHAQUE CENTRE

- Nommer dans chaque centre un responsable de la remise des questionnaires et prévoir son remplacement en cas d'absence ou de vacances.
- Prévoir un échéancier de remise des questionnaires en même temps que la randomisation dans l'étude, en remettre un double au patient et le lui expliquer.
- Chaque centre gardera une copie des questionnaires avant de les envoyer avec les fiches de l'étude.
- Mettre un double du résumé du protocole dans chaque dossier et rendre accessible le protocole complet dans chaque secteur de soins.

Appendix 8- EORTC QLQ-C30 (version 3.0)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix 9- Translational Research
Recherche de facteurs prédictifs de réponse aux anti-EGFR et anti-VEGF

Investigateur coordonnateur : Dr Marc Denis, Laboratoire de Biochimie, Institut de Biologie CHU de Nantes
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METHODES

L'étude sera basée sur la recherche de marqueurs au niveau de **la tumeur** et dans **le sérum** des patients

→ Consentement éclairé signé spécifique pour cette étude biologique.

→ Matériel biologique humain concerné : sang veineux périphérique et blocs tumoraux

→ Lieu de stockage et d'analyse :

Laboratoire de Biochimie
Institut de Biologie - CHU de Nantes
9 quai Moncousu
44093 Nantes cedex

Etude de la tumeur

Au moment de l'inclusion, nous collecterons les blocs tumoraux disponibles dans les cabinets d'anatomie et cytologie pathologiques grâce à un système de bons de transports pré-payés. A partir de ces blocs, nous préparerons une coupe colorée HES (pour vérification de l'histologie) et plusieurs lames blanches. Après sélection de la zone la plus riche en cellules cancéreuses, nous extrairons l'ADN en utilisant l'automate d'extraction iPrep (Invitrogen). Le matériel non utilisé sera réadressé au laboratoire immédiatement après avoir réalisé les coupes nécessaires. Un dédommagement de 30 € par patient sera envoyé au cabinet.

Dans le cas extrême ou les blocs ne peuvent pas être récupérés, il sera demandé aux anapaths de nous adresser 1 lame colorée pour HERS + 3 coupes 5µm (pour l'immunohisto) + 3 coupes 10µm (pour la biomol).

1. Les patients inclus dans cette étude doivent avoir un gène K-*RAS* sauvage (non muté) dans leur tumeur (1-3).
Cette première analyse sera faite au niveau des plateformes de génétique moléculaire des cancers dont dépendent les centres recruteurs. Les techniques utilisées sont différentes, et les résultats préliminaires du projet (STIC) MOKAECM (Evaluation de la Recherche des Mutations de l'Oncogène KRAS pour le traitement par les Anticorps anti-EGFR des patients porteurs d'un cancer Colorectal Métastatique) indiquent des différences de sensibilité entre les tests utilisés.

Il conviendra donc tout d'abord de **vérifier que les patients sont bien tous porteurs d'un gène K-*RAS* sauvage**.
Il sera utilisé une technique très sensible et spécifique (PCR spécifique d'allèle). Seront recherchés les mutations les plus fréquentes (codons 12 et 13) mais également les mutations plus rares (codons 61 et 146) récemment décrites comme étant associées à une inefficacité des anti-EGFR (4).

2. Seront également étudiés les marqueurs moléculaires suivants :.
   - Mutation V600E du gène *BRAF* (5, 6)
   - Mutations du gène *PIK3CA (E242K, E545 K et H1047R)* (7)

Il pourra ainsi être déterminé si ces altérations sont prédictives de l'efficacité du cétuximab ou du bevacizumab

Des méthodes semblables à celles utilisées pour K-RAS sont disponibles dans notre laboratoire (8).

- Expression des ligands de l'EGFR (amphiréguline et épiréguline) (9, 10)

Une coupe 10µ sera utilisée pour extraire de l'ARN. Les ADNc seront synthétisés selon des techniques classiques, et l'expression de ces gènes sera mesurée par RT-PCR quantitative en temps réel.

- Expression de PTEN, pAKT et MKP-1 (11, 12)

L'étude de l'expression de ces marqueurs sera faite par immunohistochimie.

3. La **méthylation de l'ADN** joue un rôle clé dans la régulation de l'expression, et notre hypothèse de travail est que la perte d'expression de certains gènes par méthylation pourrait influencer la réponse au traitement. C'est un axe de recherche peu développé et il n'existe pas de données dans la littérature associant la méthylation de certains gènes suppresseurs de tumeurs et l'efficacité des molécules comparées dans cette étude.
La disponibilité d'ADN (utilisé en petite partie seulement pour les études citées précédemment) permettra d'analyser la méthylation d'un certain nombre de gènes.
La technique de Methylation-specific – Multiplex Ligation-dependent Probe Amplification (MS-MLPA) permet d'analyser la méthylation dans des régions spécifiques de gènes. Ces études se font sur de très faibles quantités d'ADN (20 ng), ce qui est compatible avec les prélèvements qui seront à disposition.
Nous avons une expérience de ces tests : étude de la méthylation du gène *VHL* dans les cancers du rein (13), du gène *TIMP3* dans les cancers du rein (14) et du gène *hMLH1* dans les cancers colorectaux (abstract EACR 2010).
Les kits utilisés seront ceux commercialisés par la société MRC-Holland (http://www.mrc-holland.com). 4 kits sont disponibles. Il pourra ainsi déterminer si la méthylation d'un ou de plusieurs gènes est associée à l'efficacité du cétuximab ou du bevacizumab.

Recherche de marqueurs sériques

La concentration de facteurs solubles dans la circulation sanguine peut être associée à certaines caractéristiques des tumeurs et à leur évolution. Des données récentes indiquent par exemple que la concentration sérique en interleukine 8 serait un facteur prédictif de réponse au bévacizumab (15).
Dans le contexte de cette étude ou 2 thérapies ciblées seront comparées, il parait intéressant de doser dans le sérum des patients avant le traitement, des molécules susceptibles d'être des marqueurs prédictifs de l'efficacité du cétuximab ou du bevacizumab.

Un prélèvement sanguin (3 ml tube sec) sera collecté avant le début du traitement. Les tubes de sang seront à centrifuger localement (laboratoire) et les aliquots (3 x 0.5 ml) ainsi que le tube primaire seront à congeler à -80°C. Tous les tubes seront récupérés à la fin de l'inclusion.

L'analyse des facteurs solubles sera faite par technologie Luminex™. Cette technologie est fondée sur le principe de la cytométrie en flux, et allie l'utilisation de microsphères fluorescentes et une

double lecture après excitation par deux lasers. Ces différentes billes peuvent être couplées à leur surface avec différents anticorps, permettant ainsi la quantification de plusieurs molécules dans le même test.
Le panel d'anticorps disponible sur ces billes est très large (http://www/millipore.com), et nous ciblerons en première intention les molécules présentant un lien avec les thérapies comparées : EGF, sEGFR, VEGF, sVEGFR1, sVEGFR2, sVEGFR3, amphiregulin, epiregulin, IL8.
La concentration sérique de ces différentes molécules sera comparée à l'efficacité du cétuximab ou du bevacizumab.

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