UNICANCER GastroIntestinal Group

PROTOCOLE UC-0110/1209

PRODIGE 28

UCGI 27

EudraCT N° : 2012-005139-99

Randomized phase II study of first-line FOLFIRI plus cetuximab for 8 cycles followed by either single-agent cetuximab as maintenance therapy or observation in patients with wild-type KRAS and NRAS metastatic colorectal cancer

TIME (Treatment after Irinotecan-based frontline therapy: Maintenance with Erbitux)

Version n°10 of the 03/04/2023

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Submission History			
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Amendement #12	Version 10 – 03/04/2023	*Pending*	*Pending*

SYNOPSIS – PRODIGE 28 – UCGI 27

A) TRIAL IDENTIFICATION

CODE ATTRIBUTED BY THE SPONSOR : UC-0110/1209

VERSION AND DATE : VERSION N° 10 OF THE 3 APRIL 2023

TITLE: Randomized phase II study of first-line FOLFIRI plus cetuximab for 8 cycles followed by either single-agent cetuximab as maintenance therapy or observation in patients with wild-type KRAS and NRAS metastatic colorectal cancer.

ABRIDGED TITLE : TIME

PRINCIPAL INVESTIGATOR : Dr Valérie Boige, medical oncologist (Gustave Roussy; Villejuif)
ASSOCIATE PRINCIPAL INVESTIGATOR : Prof Olivier Bouché, digestive oncologist (CHU Robert Debré; Reims)

NUMBER OF PARTICIPATING CENTERS (ESTIMATE) : 60	**NUMBER OF PATIENTS :** 195

B) SPONSOR IDENTIFICATION

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C) GENERAL INFORMATION

INDICATION: First-line treatment for non resectable metastatic colorectal cancer (mCRC)

METHODOLOGY:

National multicentric phase II trial evaluating whether single agent cetuximab is effective as maintenance therapy after 8 cycles of first-line FOLFIRI plus cetuximab in mCRC patients with wild-type KRAS and NRAS assessed by progression-free survival (PFS) at 6 months after starting maintenance therapy.

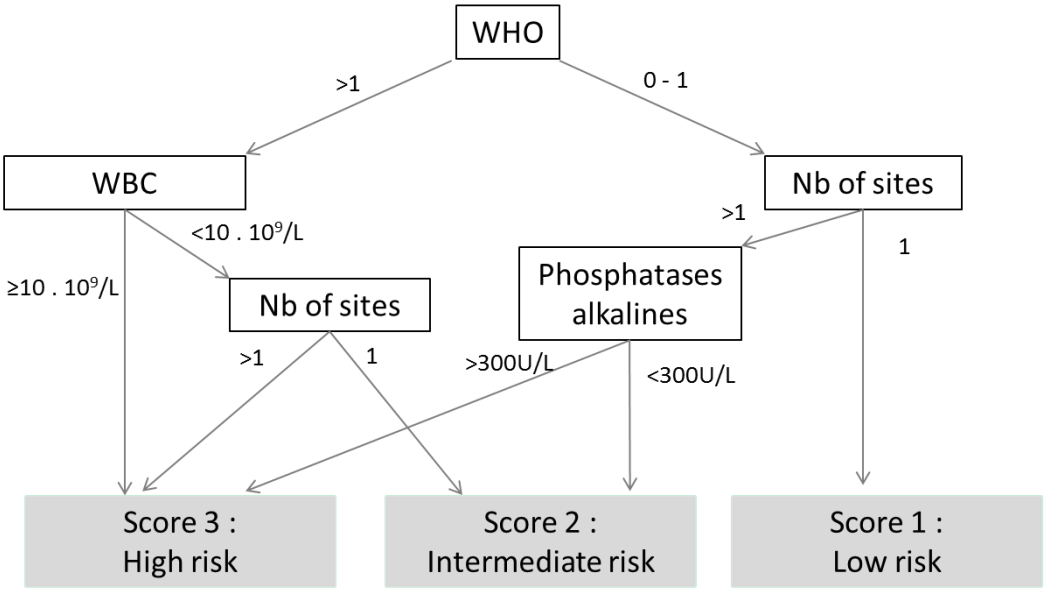
STUDY OBJECTIVE

PRIMARY OBJECTIVE To collect preliminary information concerning the efficacy of single agent cetuximab as maintenance therapy after 8 cycles of first-line FOLFIRI plus cetuximab in mCRC patients with RAS (KRAS+NRAS) wild-type tumors assessed by PFS at 6 months after starting maintenance therapy.

SECONDARY OBJECTIVES:

- Time to first-line strategy failure
- Tumor response (Objective response rate)
- Tumor response (Objective response rate) after reintroduction of FOLFIRI plus cetuximab in each arm
- Impact of early tumor shrinkage (>20% decrease on the 8-weekly radiological assessments) on long-term outcome (PFS and OS of all patients including those in phase 1)
- Predictive impact of hypomagnesemia and smoking status on treatment efficacy and outcome
- Safety (NCI CTCAE v 4.0 classification)
- Quality of life (QoL, questionnaires QLQ-C30 and QLQ-CR29)
- Overall Survival (OS) and PFS for all included patients and for randomized patients
- PFS according to prognostic factors for metastatic CRC patients: baseline CEA, LDH levels and platelet count, & Köhne Score.

Köhne et al. 2002



- Translational ancillary study to assess circulating tumor cells (CTC), circulating free tumor cell DNA, and microarray gene expression using sequential tumor biopsies to identify potential prognostic/predictive biomarkers
- PFS during the second-line of treatment

INCLUSION CRITERIA :

All the criteria listed below are required for inclusion

1) Histologically confirmed colorectal cancer
2) KRAS and NRAS wild-type genes after analysis of mutation status from the primary tumor or metastasis
3) Non resectable metastatic disease in a curative intent
4) No prior chemotherapy except for fluoropyrimidines with or without oxaliplatin-based adjuvant treatment earlier than 6 months ago from inclusion date
5) Patient presenting with at least one measurable tumor target (≥ 10 mm) according to RECIST criteria, which has never been irradiated
6) Patient with a greater than 3-month life expectancy

7) Performance Status ≤ 2 (WHO)
8) Male or female aged ≥ 18 years.
9) Laboratory requirements
- Haematology:
  - ✓ Neutrophil count ≥ 1.5 x 10^9/L
  - ✓ Platelet count ≥ 100 x 10^9/L)
  - ✓ Leucocyte count > 1500/mm^3
- Hepatic Function:
  - ✓ Total bilirubin ≤ 1.5 times the upper normal limit (UNL)
  - ✓ ASAT ≤ 2.5xUNL in absence of liver metastases, or ≤ 5xUNL in presence of liver metastases
  - ✓ ALAT ≤ 2.5xUNL in absence of liver metastases, or ≤ 5xUNL in presence of liver metastases
- Renal Function
  - ✓ Creatinine clearance (according to Cockroft and Gault formula) ≥ 50 mL/min or blood creatinine level ≤ 1.5x ULN
- Metabolic Function
  - ✓ Magnesium ≥ lower limit of normal.
  - ✓ Calcium ≥ lower limit of normal

10) Patient who has signed a written informed consent form.

NON INCLUSION CRITERIA

One of the following criteria is sufficient for non inclusion:

1) Known and/or symptomatic brain metastases
2) Known allergy to one of treatment components
3) Neurological or psychiatric condition which could interfere with good treatment compliance
4) Patient currently in treatment with any other anti-tumor therapy: chemotherapy or targeted therapy or radiotherapy ≤14 days before randomization
5) Other serious conditions such as: respiratory failure. History of interstitial lung disease e.g. pneumonitis or pulmonary fibrosis or evidence of interstitial lung disease on baseline chest CT scan.
6) Clinically significant cardiovascular disease (including myocardial infarction, unstable angina, symptomatic congestive heart failure, serious uncontrolled cardiac arrhythmia) ≤12 months before enrolment or randomization
7) Concomitant severe infection.
8) History of cancer (except skin cancer other than melanoma or an in situ cervical epithelioma or other solid tumor treated for curative purposes without signs of the condition and with no treatment administered in the 5 years before randomization.)
9) Patient already included in another clinical trial with an investigational molecule
10) Prior treatment with anti-EGFr antibodies (e.g. panitumumab (Vectibix®) or cetuximab / Erbitux®) or treatment with small EGFr inhibitor molecules (e.g., erlotinib / Tarceva®)
11) Pregnant female, likely to be or currently breast feeding, or planning to become pregnant within 6 months after the end of treatment or absence of effective contraception for males and females of childbearing age during treatment and for 6 months (male or female) after the end of treatment
12) Those deprived of their freedom or under guardianship
13) Impossibility of undergoing trial's medical follow-up for geographical, social or psychological reasons

CRITERIA FOR EVALUATION:

Tumor response and progression will be assessed by CT scan according to RECIST criteria version 1.1.

Primary endpoint

Disease control rate: Progression Free Survival (PFS) at 6 months after the start of maintenance therapy defined as the number of patients at 6 months from the date of randomization without documented progression or death from any cause. Progression will be assessed by CT scan

according to RECIST criteria version 1.1

Secondary endpoints

Efficacy

- Time to first-line strategy failure defined by time between randomization and disease progression during reintroduced FOLFIRI-cetuximab in both arms, first-line strategy discontinuation (for limiting toxicity or patient choice), or death during first-line strategy

  Time to first-line strategy failure including the Phase 1 will be also assessed in the randomized patient population
- The objective response rate before randomization is defined as the percentage of subjects with a complete response (CR) or partial response (PR) confirmed by investigator assessment as per RECIST criteria version 1.1
- Objective response rate defined as complete response (CR) or patial response (PR) according to RECIST criteria version 1.1.
- Progression-Free Survival (PFS) of the randomized study population is defined as the time from the date of randomization to the date of the first documented progression or any cause of death during the study. Progression will be assessed by CT scan according to RECIST criteria version 1.1
- Progression Free Survival (PFS) of the overall included study population is defined as the time from the date of inclusion to the date of the first documented progression or any cause of death during the study. Progression will be assessed by CT scan according to RECIST criteria version 1.1
- Overall Survival (OS) of the randomized study population is defined as the time from the randomization to the date of documented death
- Overall Survival (OS) of the overall included study population is defined as the time from the inclusion to the date of documented death
- Safety according to the NCI CTCAE v 4.0 classification

  Safety of the study treatments will be assessed on occurrence of adverse events (AEs), intake of concomitant treatments, changes arising during active treatment in physical examination, vital signs (blood pressure, pulse rate and body temperature), ECG, and clinical laboratory tests (biochemistry, haematology). Safety parameters will be graded based on NCI CTCAE v 4.0 classification
- Quality of life assessed by QLQ-C30 and QLQ-CR29
- PFS during second-line treatment defined as the time from second-line initiation to the date of documented progression or any cause of death.

RANDOMIZATION:

Randomization will be stratified by the following factors:

- OR (Objective response) vs SD (Stable disease)
- site
- baseline CEA (<100 µg/l vs ≥100 µg/L)
- baseline platelet count (<400 000 /µL vs ≥400 000 /µL
- Köhne Score (1 vs 2 vs 3) (it comprises WBC: <10 000 /µL vs ≥10 000 /µL, alkaline phosphatase: <300 UI/L vs ≥300 UI/L, WHO Performance Status: 0 vs ≥1 and number of metastatic sites: 1 vs >1) (Protocol - Appendix 9)

D) INVESTIGATIONAL PRODUCTS

DRUGS :

Drug name (DCI/INN)	Registered name (1)	Pharmaceutical form	Administration	Posology/dosage
Cetuximab	Erbitux®	Solution for injection	IV	**500 mg/m²**, every 2 weeks.

THERAPEUTIC REGIMENS:

PHASE 1 AT INCLUSION

Treatment to be started in the entire study cohort (Phase 1): FOLFIRI and cetuximab every 2 weeks as follows:

- Cetuximab: 500 mg/m^2 IV infusion starting with 120 min for the 1st infusion (infusion rate must not exceed 5 mg/min), 90 min for the 2nd dose (infusion rate must not exceed 10 mg/min) and subsequently a minimum of 60 min (infusion rate must not exceed 10 mg/min) if infusions are well tolerated) on D1 of each cycle.

One hour after the end of the cetuximab perfusion:

- Irinotecan 180 mg/m^2 IV infused over 90 minutes.
- Leucovorin 400 mg/m^2 (or 200 mg/m^2 of L-leucovorin) IV infused over 2 h (concurrently with irinotecan via separate infusion line).
- 5-FU 400 mg/m^2 IV bolus injection (following leucovorin administration), then 2400 mg/m^2 continuous IV infusion over 46-48 h.

Cycles will be repeated every 2 weeks

- Systematic preventative treatment for cetuximab -induced skin toxicity and infusion related reactions in both arms.
- Tumor assessment by computed tomography scans will be done within 30 days before inclusion and then repeated every 8 weeks (tumor response according to RECIST).

STEP 2: RANDOMIZATION AT 16 weeks

In case of objective response or stable disease after 8 cycles (16 weeks) ➔ Randomization

Arm A: cetuximab 500 mg/m^2 alone every two weeks until disease progression. FOLFIRI plus cetuximab will be reintroduced for 8 cycles (16 weeks) in case of disease progression during cetuximab maintenance. This therapeutic strategy will be repeated in case of objective response or stabilization obtained during the 8 cycles of FOLFIRI + cetuximab or stopped in case of disease progression under FOLFIRI plus cetuximab.

Arm B: observation until disease progression. FOLFIRI plus cetuximab will be reintroduced for 8 cycles (16 weeks) in case of disease progression during the treatment-free interval (observation). This therapeutic strategy will be repeated in case of objective response or stabilization obtained during the 8 cycles of FOLFIRI + cetuximab or stopped in case of disease progression under FOLFIRI plus cetuximab.

In case of disease progression after FOLFIRI-cetuximab reintroduction, it is recommended that the patient receives second-line chemotherapy containing oxaliplatin and bevacizumab.

TREATMENT DURATION: until progression

The study treatment will be discontinued in case of:

- Progressive disease
- Limiting toxicity
- Investigator's or patient's decision

E) STATISTICAL DESIGN

REQUIRED NUMBER OF PATIENTS:

A total of 134 randomized patients are required

- 45%-50% patients will present with a KRAS and or NRAS mutation at initial screening who will therefore not be able to be enrolled in the study, only RAS (KRAS + NRAS) wild-type patients will be enrolled.

- Median first-line PFS of patients with RAS wild-type tumors treated with chemotherapy combined with anti-EGFR monoclonal antibodies is about 9 months according to several recent phase III trials.

- Data from studies of KRAS wild-type patients show that about 20% patients will have progressive disease after 4 months of FOLFIRI + cetuximab. We estimated that the median first-line PFS of KRAS patients after the beginning of treatment would reach 10 months (= 6 months after randomization in the present study, giving a 6-month PFS rate of 50% after starting maintenance treatment).

- Results of the COIN B trial of KRAS wild-type patients showed that the median first-line PFS calculated from the 12th week (after 3 months of FOLFOX + cetuximab) is about 6 months in the maintenance treatment cetuximab arm, and 3 months in the intermittent treatment cetuximab arm (no treatment until progression). The 3 months shorter PFS in the intermittent cetuximab arm is partially compensated by reintroduction of the combination treatment at progression (failure-free survival: 12 versus 14 months).

- The population of this study is subsequently restricted to RAS wild-type patients with about a 2 months longer median PFS than in KRAS wild-type patients (according to updated results of FIRE3 in 2014 and CALGB studies, in this study, 8 months after randomization). The PFS rate at 6 months after the randomization is estimated at 60%.

- The sample size is based on the Fleming single stage design (target one-sided alpha=5%, actual alpha=7.8%, target beta=20%, actual beta=14.3%). It will be concluded that cetuximab alone as maintenance is effective if the 6-month PFS rate in arm (A) is higher than or equal to 55% and to conclude it is ineffective if the 6-month PFS rate is lower than or equal to 40%. Sixty seven patients have to be included in the experimental arm (A), and a total of 134 evaluable randomized patients are required.
  [Fleming TR. One sample multiple testing procedure for phase II trials. Biometrics 1982; 38:143-151].

  It should be noted that the alpha level is set at 5% (one-sided), equivalent to level of risk of concluding 'efficacy' ($p > p0$) when there is actually no efficacy ($p \leq p0$), and with the beta set at 20%, the risk of concluding an absence of efficacy ($p < p1$) when there is actually noteworthy efficacy ($p \geq p1$).

  Cetuximab alone arm (A): -if less than 34 patients (out of the 67) are alive without progressive disease at 6 months after randomization, the conclusion will be that cetuximab alone is ineffective. -If 34 or more patients (out of the 67) are alive without progressive disease at 6

months after randomization, the conclusion will be that cetuximab alone is effective.
Observation arm (B): Patients receiving no treatment constitute an internal control group to validate the hypothesis of a 6-month PFS of 40%. The 95% confidence interval (CI) of the 6-month PFS rate will be calculated. If 40% is included in the 95% CI, the conclusion of the study will be interpreted according to the Fleming' decision rule. If 40% is not included in the 95% CI, the conclusion of the study will be interpreted as follow:

Group B	**Group A conclusion**	
95%CI of the 6-monthPFS rate	**Cetuximab alone effective**	**Cetuximab alone ineffective**
40% < 95%CI lower limit	Results to be discussed	Fleming's Conclusion
40% included in the 95%CI	Fleming's Conclusion	Fleming's Conclusion
40% > 95%CI upper limit	Fleming's Conclusion	Results to be discussed

- Considering that a maximum of 30% patients will have progressive disease after 4 months of FOLFIRI + cetuximab, we have to include 61 more patients. **Therefore a total of 195 patients have to be included in the trial.**
-

- **Randomization stratification**:
  - OR (Objective response) vs SD (Stable disease)
  - Site
  - baseline CEA (<100 µg/L vs ≥100 µg/L)
  - baseline platelet count (<400 000 /µL vs ≥400 000 /µL)
  - Köhne Score (1 vs 2 vs 3) (it comprises WBC: <10 000 /µL vs ≥10 000 /µL, alkaline phosphatase: <300 UI/L vs ≥300 UI/L, WHO Performance Status: 0 vs ≥1 and number of metastatic sites: 1 vs >1).

STATISTICAL ANALYSIS :
The primary endpoint will be progression-free survival at 6 months.

Descriptive statistics are planned for the secondary endpoints.

The PFS, time to first-line strategy failure, and OS will be estimated with the Kaplan-Meier method and survival estimates at 6 months and 1 year will be calculated with their associated CI95% confidence intervals.

F) TRANSLATIONAL RESEARCH

Circulating tumor cells (CTC) and free tumor cell DNA quantification in blood samples at 4 time points:

1/ Baseline: before the initiation of chemotherapy with FOLFIRI plus cetuximab in all patients
2/ After 4 months of FOLFIRI plus cetuximab in all patients (at randomization, just before maintenance therapy or observation)
3/ 1 month after randomization in each arm (after one month of maintenance therapy or observation)
4/ At progression in each arm

Aims:

1/ To assess the prognostic and predictive value of circulating CTC and free tumor DNA
We hypothesized that CTC counts and free tumor DNA detection could serve as prognostic and predictive biomarkers (prediction of response and/or early progression).
CTC absolute values and cell-free tumor DNA quantification at each time point will be analyzed for relationship with tumor response and PFS.
We plan to analyze the patient outcome according to threshold value of 3 free CTCs per 7.5 mL (two groups : ≥3 CTC/7.5 mL versus <3 CTC/7.5 mL) according to previous published data

on CTC in advanced colorectal cancer). We assume that 30% of the patients will be find to have a CTC count above 3/7.5 mL, according to previous data (Tol J et al. Ann Oncol 2010; 21:1006-12)
The mean concentration of free circulating DNA measured in plasma using a quantitative PCR assay is around 200ng/ml in patients with cancer and 4ng/mL in healthy subjects.
2/ To determine and compare the sensitivity of CTC and cell-free tumor DNA detection in patients with advanced CRC
3/ To determine and compare the characterization of tumor-associated molecular alterations in the circulating free tumor DNA and in the tumor

Fixed and frozen sequential tumor biopsies (one before FOLFIRI-cetuximab introduction, and one at progression) for biomarker analysis including

- intratumor expression of downstream signaling phosphoproteins of the EGFR and PI3K/AKT pathways,

Genome array analysis on frozen tissue samples to identify a gene expression signature predictive of response and/or resistance to FOLFIRI plus cetuximab. The aim of this analysis is to identify activation of molecular pathways involved in tumor response and acquired resistance to cetuximab and FOLFIRI detected either in pre- or per-treatment tumor samples

G) TRIAL DURATIONS
INCLUSION PERIOD: 4.5 years
TREATMENT DURATION: until progression
FOLLOW-UP PERIOD: 2 years
EXPECTED TRIAL DURATION BEFORE THE MAIN OBJECTIVE IS ANALYZED: 6.5 years
OVERALL TRIAL DURATION (INCLUDING FOLLOW-UP): 7.5 years

H) TREATMENT MONITORING AND EXAMINATION SCHEDULE

	Period prior to treatment		Period of treatment by FOLFIRI-cetuximab (Initial and during reintroductionof the FOLFIRI-cetuximab), after PFS1 and until PFS2	End of initial 16 week treatment phase	Maintenance period (Arm A & B)	Evaluation at progression (P1) during the less intense therapeutic phase	Evaluation at progression (P2) after the reintroduction of FOLFIRI-cetuximab	End of Study	Follow up after PFS2	Follow up during following lines of treatments
	Selection	Baseline Visit	Every 2 weeks during the 16 weeks		Every 2 weeks until disease progression				Every 8 weeks	Every 8 weeks
Allowed visit date range			± 3 days		± 3 days				± 1 week	± 1 week
Patient visit	X	X	X	X	X	X	X	X	X	X
Informed consent	X									
Medical History	X									
Inclusion/exclusion	X	X								
Évaluation for randomization				X						
Randomization				X						
Tabaco consumption	X									
Genetic mutation	X	X								
EVALUATION OF THE TUMOR										
CT scan (RECIST)		X	Every 8 weeks		Every 8 weeks	X	X		X	X
EVALUATION OF THE QUALITY OF LIFE										
Quality of life questionnaires EORTC QLQ-C30 and CR29		X	Every 8 weeks		Every 8 weeks			X		
Performance status WHO		X	X	X	X			X		
EVALUATION OF THE TOXICITY										
Adverse Events			X	X	X	X		X		
Concommitant medication		X	X	X	X			X		
Physical Examination		X	X	X	X			X		
Vital signs		X	X	X	X			X		
Tumor biomarker : CEA		X	Every 8 weeks	X	Every 8 weeks	X				
CBC (Leucocytes, Neutrophiles, Hb, Plaquettes, Hematies)		X	X	X	X					
Hepatic Evaluation (ALP, bilirubin total, conjugated,free, ASAT, ALAT, GGT)		X	X	X	X					
Blood ionogram + electrolytes (Creatinine clearance, urea, Ca, Mg)		X	X	X	X	X				
LDH		X	every 8 weeks		every 8 weeks					
Urine tests		X	X		X					
ECG		X								
Pregnancy test		X								
DELIVERY OF THE STUDY TREATMENT										
Cetuximab					X in Arm A					
Cetuximab +FOLFIRI			X							
Following chemotherapies									X	X
FOLLOW UP										
Vital status									X	X
TRANSLATIONAL RESEARCH										
Blood sample		X[a]		X[a**]	X[a]	X[a]				
Tumor biopsy [b]		X[b]					X[b***]			

Follow up of patients who withdraw prematurely from the study due to tumor progression or toxicity will be maintained every 8 weeks until death; (1) and (2) First Progression and second progression

[a]Evaluations for the blood samples: D1 (before treatment), after 4 months of initial Folfiri+cetuximab, J30 (after randomization) and at progression during maintenance or observance (reduced intensity treatment phase).

[b]optional tumor and health tissue biopsies before treatment and tumor biopsy only at progression with FOLFIRI–cetuximab. *only the magnesium every 8 weeks; **applicable to included patients not eligible for randomization; ***Applicable to patients not eligible for randomization due to initial progression with FOLFIRI-cetuximab

TABLE OF CONTENT

ABBREVIATIONS

AE	Adverse Event
AFSSAPS	Agence Française de Sécurité Sanitaire des Produits de Santé
ALAT, ALT (SGPT)	Alanine aminotransferase
ALP	Alkalin phosphatase
ANC	Absolute neutrophil count
ANSM	Agence Nationale de Sécurité du medicament (French Competent Authority)
ASAT, AST (SGOT)	Aspartate aminotransferase
AUC	Area under the serum concentration-time curve
BRC	Biological Resource Center
CBC	Complete Blood Count
CEA	Carcino-Embryonic Antigen
COS	Comité d'Orientation Stratégique
CPP	Committee for Protection of Persons
CR	Complete response
CRA	Clinical Research Associate
CRB	Centres de Ressources Biologiques
CRF	Case report form
CRO	Contract Research Organization
CT	Computerized tomography
CTCAE	Common terminology criteria for adverse events
CYP	Cytochrome P450
DSMB	Data Safety Monitoring Board
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic Case report form
ECOG	Eastern Cooperative Oncology Group
EGF	Epidermal Growth Factor
EGFR	Epidermal Growth Factor Receptor, also known as ErbB1 or HER-1
EMA	European Medicines Agency
EORTC QLQ-C30	European organization for Research and Treatment of Cancer Quality of Life Questionnaire
ErbB1	EGFR, c-ErbB1; HER-1
ErbB2	c-ErbB2, also known as HER-2/neu
FDA	Food and Drug Administration
FCPRCC	Federation of the Patient Committees for Clinical Research in Cancerology
g	Grams
GCP	Good Clinical Practice
Hb	Hemoglobin
HER1, 2, 3, 4	Human Epidermal Growth Factor Receptor Class I tyrosine kinase receptor(s) (Synonymous with erbB1-4)
HR	Hazard ratio
IB	Investigator Brochure
IDN	International Drug Name
IFL	Irinotecan 5-fluorouracil leucovorin
IHC	Immunohistochemistry
ILD	Interstitial lung disease
INR	International normalized ratio
IP	Investigational Product
ITT	Intent-to-treat
IV	Intravenous
L	Liter
LD	Longest diameter
LNCC	National League for Treating Cancer

L-VEF	Left Ventricular Ejection Fraction
mg	Milligram(s)
mins	Minutes
ml	Milliliter(s)
MTD	Maximum tolerated dose
NCI	National Cancer Institute
nM	Nanomol
NSCLC	non–small cell lung *cancer*
OS	Overall survival
PD	Progressive disease
PD	Pharmacodynamic
PFS	progression-free survival
PK	Pharmacokinetics
PR	Partial response
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
SAE	Serious adverse event
SBP	Systolic Blood Pressure
SD	Stable disease
SPC	Summary of Products Characteristics
SUSAR	Suspected Unexpected Serious
TDM	Tomodensitometry
TTP	Time to progression
ULN	Upper limit of normal
US	United States
WBC	White Blood Cell

UNICANCER the study sponsor declares that the PRODIGE 28 - UCGI 27 trial will be conducted in accordance with this protocol, the Code de la Santé Publique articles 1121-1 and the related decretes and orders in force as well as the Good Clinical Practices (GCP) as defined on November 24, 2006.

1. INTRODUCTION AND RATIONALE OF THE STUDY

1.1. Study Rationale

1.1.1 Epidemiology of CCRm

In the European Union, about 300,000 new cases of colon and rectal cancers were detected in 2006 with about 140,000 deaths (**1**). In the United States, an estimated 148,000 new cases of colon and rectal cancer were expected in 2008, representing 10% of the new cancer cases. The number of deaths estimated was about 50,000, accounting for 9% of all cancer deaths. It is the third most common cancer in both men and women (**2**). Mortality rates have declined in the past decades, reflecting both declining incidence rates and improvements in early detection and treatment. More than 90% of cases are diagnosed in individuals aged 50 and older. The risk of colorectal cancer is increased by certain inherited genetic mutations, a personal or family history of colorectal cancer/polyps or a personal history of chronic inflammatory bowel disease (**2**).

1.1.2 Prognosis

The 1- and 5-year relative survival for colorectal cancer patients is 82% and 64%, respectively. Survival continues to decline beyond five years to 57% at 10 years after diagnosis. However, the chance of survival varies considerably, depending of the cancer stage at diagnosis. When the cancer is detected at an early, localized stage, the 5-year survival is 90%. After the cancer has spread regionally to involve adjacent organs or lymph nodes, the 5-year survival drops to 68%. For patients with distant metastases, the 5-year survival is less than 10%.

1.2. Chemotherapy: literature background

1.2.1 Drug profile

Cetuximab is a recombinant human-mouse chimeric monoclonal antibody which binds specifically to the epidermal growth factor receptor (EGFR, HER1, c-ErbB-1). Cetuximab is composed of a murine Fv (EGFR-binding) region and a human IgG1 heavy and kappa light chain Fc (constant) region. In vitro studies have shown that cetuximab competes with endogenous ligands for binding on the external domain of the EGFR. Cetuximab binds to the EGFR with 10-fold higher affinity than endogenous ligands (0.1−0.2 nM versus 1 nM, cetuximab versus EGF or TGF-a, respectively) (**1**,**3**). Binding of cetuximab to the EGFR blocks phosphorylation and activation of receptor-associated kinases, resulting in inhibition of cell growth, induction of apoptosis, inhibition of angiogenesis, tumor cell invasion and metastasis and augmentation of the effects of chemo- and radiotherapy. Cetuximab also induces receptor dimerization and internalization thus resulting in an overall downregulation of the EGFR. In vitro, cetuximab can mediate antibody-dependent cellular cytotoxicity (ADCC) against certain human tumor types. Furthermore, the addition of cetuximab to chemo- and radiation therapy has been shown to overcome previous resistance to chemo- or radiotherapy (R09-1571). Of note, cetuximab can increase signalling inhibition of small molecule tyrosine kinase inhibitors in vitro and that, despite targeting the same receptor, cetuximab and small molecule tyrosine kinase inhibitors have non-overlapping mechanisms of action (**2**)

Cetuximab demonstrates nonlinear saturable kinetics when used as monotherapy or in combination with concomitant chemotherapy or radiotherapy. The area under the concentration time curve (AUC) increased in a greater than dose proportional manner while clearance of cetuximab decreased from 0.08 to 0.02 L/h/m^2 as the dose increased from 20 to 200 mg/m^2, and at doses >200 mg/m^2, it appeared to plateau. The volume of the distribution for cetuximab appeared to be independent of dose and approximated the vascular space of 2-3 L/m^2.

Following the approved dose regimen (400 mg/m^2 initial dose; 250 mg/m^2 weekly dose), concentrations of cetuximab reached steady-state levels by the third weekly infusion with mean peak and trough concentrations across studies ranging from 168 to 235 and 41 to 85 µg/mL, respectively. The mean half-life of cetuximab was approximately 112 hours (range 63–230 hours). The pharmacokinetics of cetuximab were similar in patients with squamous cell cancer of the head and neck (SCCHN) and those with colorectal cancer.

Cetuximab does not appear to exhibit pharmacokinetic drug interactions with gefitinib, cisplatin, carboplatin, irinotecan, docetaxel or fluorouracil (**2,3**)

In the U.S., cetuximab is indicated for the treatment of squamous cell cancer of the head and neck in

combination with radiotherapy in the local/locally advanced setting and in the recurrent/metastatic setting after failure of platinum-containing regimens; it is also indicated for the treatment of metastatic colorectal cancer either as a single agent or in combination with irinotecan. Similarly, in Europe, cetuximab is indicated for the treatment of patients with EGFR-expressing, RAS wild-type metastatic colorectal cancer and patients with squamous cell cancer of the head and neck.
The only clinical trial of cetuximab as monotherapy in NSCLC showed a very low efficacy result (5% response rate) compared with the EGFR-TKIs (**4**) Combination of cetuximab with cytotoxic chemotherapy in EGFR-expressing advanced NSCLC demonstrated a modest improvement in response and OS (**5**)

1.2.2 Rationale

(1) Progress in the management of advanced or metastatic colorectal cancer

In a decade and a half of research, with the introduction of more effective cytotoxic drugs such as oxaliplatin and irinotecan associated with either 5-fluorouracil (5-FU) or capecitabine and, more recently, combined with targeted therapies (bevacizumab, cetuximab) significant progress has been made in the management of advanced/metastatic colorectal cancer pushing back the survival limit of a pathology for which no real therapeutic approach existed before (**1-5**).

Gradually, the use of chemotherapy has shifted from purely palliative care to disease control intent and the efficacy of the 1st line experimental treatment is continuously gaining momentum with median overall survival (OS) around or above 24 months in the most recent trials (6, Glimelius 2012). Two multidrug regimens: (1) folinic acid, 5-FU plus oxaliplatin (FOLFOX) and folinic acid, 5-FU plus irinotecan (FOLFIRI) are the current standard treatments (**12, 13**). The optimum integration of the these two regimens with targeted biological agents such as bevacizumab or, more recently, cetuximab and panitumumab (two monoclonal antibodies targeting the EGF receptor) is still under evaluation.
Monoclonal antibodies targeting the EGF-receptor (EGFR) combined with cytotoxic chemotherapy increase the objective response rate (ORR) and/or progression-free survival (PFS) as 1st, 2nd, and 3rd-line treatment in patients with advanced colorectal cancer [Van Cutsem E. NEJM 2009; Douillard JY. JCO 2010;Cunningham D. NEJM 2004;Sobrero A. JCO 2008; Peeters M. JCO 2010; Maughan T. Lancet 2011] Furthermore, the antitumor activity of anti-EGFR monoclonal antibodies has been also demonstrated in chemorefractory advanced CRC as 3rd-line monotherapy [Van Cutsem E. JCO 2007; Cunningham D. NEJM 2004]. Lack of benefit anti-EGFR antibody has been demonstrated in patients with advanced colorectal cancer with somatic KRAS mutation regardless of treatment line.

(2) Strategy of alternating regimens to increase tolerance and prolong the time on treatment

The optimal duration and content of 1st line therapy in pts with metastatic colorectal cancer (mCRC) once they have achieved the maximal response remains controversial. To optimize the duration and maintain the quality of life of the 1st line treatment, discontinued chemotherapy (stop and go) schedules have been attempted where chemotherapy is restarted either after a predefined period or at disease progression (**14-16**). This approach relies on experimental studies from the early 2000s that have indicated that an alternating chemotherapy regimen could delay the appearance of cell resistance and thus reduce the therapeutic load for patients (**17**).

In the GERCOR French group trial, standard FOLFOX4 administered continuously was compared with FOLFOX7 for six courses, followed by a simplified 5FU-based maintenance therapy without oxaliplatin pursued for 6 months before FOLFOX7 was reintroduced for six additional courses (OPTIMOX 1) (**18**). Duration of disease control (DDC) was the primary end point of the study. At a median follow-up of 31 months, efficacy was deemed comparable in the two arms in terms of DDC (9 vs. 10.6 months) as well as OS, PFS and response rate.
The OPTIMOX2 trial has evaluated the therapeutic benefit of oxaliplatin reintroduction after 5-FU based maintenance therapy compared directly with the same regimen without maintenance therapy (**21**). The results were also rather disappointing with conflicting discussions regarding the benefit of intermittent chemotherapy as compared with the maintenance strategy. The final conclusion of this study was that the planned complete discontinuation of antiproliferative therapy had a negative impact on DDC and also on PFS (**22**). However, the chemotherapy-free interval (CFI) started after only 3 months of therapy which may have been too short. Furthermore, chemotherapy was stopped after six cycles in all patients, thus including approximately 20% of the patients in whom it might have been considered inappropriate to stop chemotherapy (progressive disease or curative surgery after a substantial tumor response). Despite the

results of this study, chemotherapy discontinuation could be safely considered for selected patients, but the CFI cannot be prescheduled before therapy commences, because individual responses cannot be predicted. For this reason, randomization before the starting chemotherapy is probably inappropriate.

Data concerning irinotecan-based chemotherapy are scarce. In the multicenter randomized GISCAD trial involving 337 patients recruited in 27 institutions, intermittent chemotherapy (arm A) with levo-leucovorin + 5-fluorouracil (5-FU) + irinotecan (CPT) (FOLFIRI) was compared with the same regimen given continuously (arm B) (**19**. Labianca Annals of oncology, 2010). Both treatments were administered until progression; every 2 weeks, 2 months on and 2 months off in arm A and every 2 weeks continuously in Arm B. The study was designed to assess the noninferiority of the intermittent arm with respect to the primary end point of OS. At a median follow-up of 41 months, OS was 18 months in arm A and 17 months in arm B [hazard ratio (HR), 0.88]. PFS was also comparable between the two groups (6 months in both arms), and even the rate of grade 3–4 toxicities (mainly myelosuppression, fever and diarrhoea) was similar. However, the authors indicated the possibility of shortcomings in the trial methodology and results. Noninferiority was evaluated by comparison of OS instead of PFS which allows a more direct evaluation of disease control, a lower objective response rate was reported in the intermittent arm versus the continuous arm (50% vs. 60%) and a higher percentage of patients received second line chemotherapy compared with the registration trial of irinotecan (**20** Douillard et al. Lancet 2000).

The MRC COIN study randomized phase III trial has compared an oxaliplatin-based continuous schedule (FOLFOX) with the same regimen administered intermittently with a chemical-free interval until disease progression. More than 1600 patients were randomly assigned to receive either continuous oxaliplatin and fluoropyrimidine combination (arm A), continuous chemotherapy plus cetuximab (arm B), or intermittent (arm C) chemotherapy. In the per-protocol population (arm A, n=467; arm C, n=511), median survival was 19.6 months in arm A and 18.0 months in arm C (HR =1.087, CI95%[0.986–1.198]). The upper limits of CIs for HRs in both analyses were greater than the predefined non-inferiority boundary (**23**).

Overall, although non-inferiority of intermittent compared with continuous chemotherapy could not be demonstrated in the COIN trial, results from both optimox 2 and COIN trials showed that chemotherapy discontinuation can be safely considered for selected patients offering reduced time on chemotherapy, reduced cumulative toxic effects, and improved quality of life. However,the shortcoming of this strategy is the impossibility to reliably pre-planned the CFI duration. The fact is that chemoresistance and response duration cannot yet be predicted in a patient population with heterogeneous physiology and tumor molecular biology. (**24-26**). One possible way to circumvent this shortcoming and allow experimental trials to keep on progressing is to randomize patients after more than 3 months of chemotherapy to exclude poor prognostic and/or non-responder patients in whom chemotherapy discontinuation appears inadequate.

(3) <u>Introducing targeted therapy with cetuximab as maintenance treatment between two intermittent chemotherapy cycles in patients with tumor expressing wild-type KRAS</u>

Despite the disappointment regarding the lack of convincing results on the benefit of treatment holidays in the 1st line treatment of mCRC, the research focus is shifting rapidly toward a modified strategy exploring intermittent schedules where CFI is replaced by a maintenance monotherapy using a less aggressive agent. One possibility is to use a targeted biological agent such as cetuximab that has proven its efficacy and safety in irinotecan-refractory metastatic CRC and in 1st, 2nd, and 3rd line therapeutic settings (**27-30**).

Cetuximab like bevacizumab is a monoclonal antibody. However, instead of VEGF, cetuximab targets the epidermal growth factor receptor (EGFR) another receptor present at the surface of tumor cells. EGFR is commonly expressed in CRC but not in most normal tissues, raising the possibility that it could serve as a target for highly selective therapy (**27**,**28**) with the ability to directly target tumor cells and thereby target micrometastasis in which angiogenesis has not yet occurred. This might confer on cetuximab a specific advantage as a maintenance treatment to prevent the development of new metastases. Furthermore, monoclonal antibodies targeting EGFR have been shown to be effcicient as a single agent in chemorefractory CRC patients [Van Cutsem E. JCO 2007; Cunningham D. NEJM 2004].

The successful result of the continuous regimen IFL + bevacizumab has suggested that a similar approach could be evaluated with cetuximab combined with FOLFOX. The MRC COIN phase III study including 1630 patients has compared the continuous administration of FOLFOX plus cetuximab versus FOLFOX (**31**). One attracting particularity of this trial was that 80% of tumors were analyzed to detect the presence of mutations in relevant biomolecular markers, principally in KRAS for which 43% mutations were

recorded, BRAF (8%) and NRAS (4%). It has been shown that KRAS mutation was associated with impaired response to anti-EGFR monoclonal antibodies (**34**). KRAS mutations were the focus of attention because they are supposed to impair the part of the protein recognized by cetuximab at the surface of tumor cells and, therefore, imply a weaker responsiveness to it (**30**). Unfortunately and quite surprisingy, continuous FOLFOX + cetuximab did not confer any OS or PFS additional benefit, either in patients with wild-type *KRAS* – the sub-group that had been predicted to be the most likely to benefit – or in the complete cohort. Only the overall objective response rate (ORR) was significantly improved in patients with KRAS wild-type tumors in the cetuximab arm compared with the control arm (57% vs. 64%, p=0.049) proving that cetuximab was active in this particular subgroup.

The impossibility to reproduce with cetuximab the synergy obtained with bevacizumab might be due to its different profile of biological activity (EGFR vs. VEGF) (**36**). It might also be due to the association with oxaliplatin and the reason why improved ORR did not translate into longer survival in the oxaliplatin-based regimen would require a deeper understanding of the mechanism of interaction of these agents with the tumor cells (**31**). Nevertheless, this negative result cannot preclude that cetuximab should be tested as well in combination with other chemotherapy regimens such as FOLFIRI to which it can be safely associated (**30**).

The hypothesis that maintenance monotherapy using a targeted agent such as bevacizumab or cetuximab may be active in mCRC is gaining momentum with the results of a phase III study presented at the American Society in Clinical Oncology (ASCO) in June 2010 (**37**). The PRODIGE 9 phase III trial was initiated to verify this finding for bevacizumab associated to FOLFIRI (**38**). Preliminary data from the COIN B trial suggest a benefit from cetuximab as maintenance therapy in terms of FFS (failure-free survival), PFS and OS, as compared with observation (treatment break) until progression after 12 weeks of first-line therapy with FOLFOX+cetuximab in patients with wild-type KRAS mCRC (**39**).

Recently, several phase III studies have shown no benefit from treatment with an anti-EGFR associated with FOLFOX or FOLRIRI in patients with CRC with rare mutations of KRAS (exons 3 and 4) and mutations of NRAS which represent approximately 10% more patients for which this treatment is not recommended [Douillard JY et al. NEJM 2013 S. Stintzing ESMO 2013].

We propose this multicenter, randomized phase II study to evaluate the efficacy and tolerability of 1st line intermittent FOLFIRI plus cetuximab with either single-agent cetuximab as maintenance biotherapy or observation intercalated between chemotherapy courses in patients with wild-type RAS metastatic colorectal cancer.

1.3. Study population

The study population aged 18 years who are affected by metastatic colorectal cancer

2. STUDY OBJECTIVES

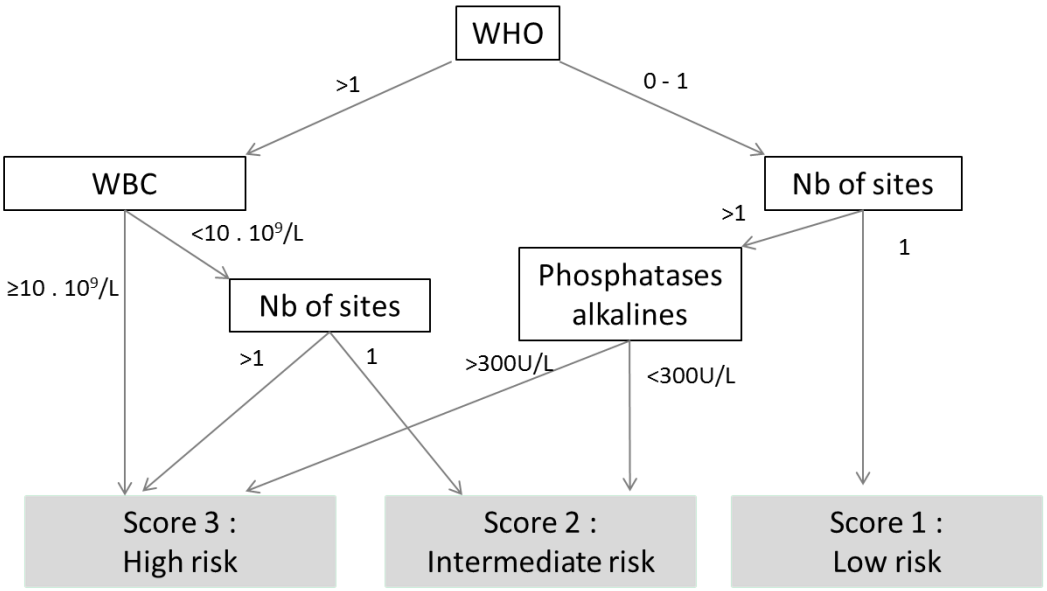
2.1. Main objective

To collect initial information as to whether single agent cetuximab is effective as maintenance therapy after 8 cycles of first line FOLFIRI plus cetuximab in mCRC patients with KRAS and NRAS wild-type assessed by progression-free survival at 6 months after the start of maintenance therapy.

2.2. Secondary objectives

- Time to first-line strategy failure
- Tumor response (Objective response rate)
- Tumor response (Objective response rate) after reintroduction of FOLFIRI plus cetuximab in each arm
- Impact of early tumour shrinkage (>20% decrease on the 8-weekly radiological assessments) on long-term outcome (PFS and OS of all included patients including step 1)
- Predictive impact of hypomagnesemia and smoking status on treatment efficacy and outcome
- Safety (NCI CTCAE v 4.0 classification)

- Quality of life (QoL, QLQ-C30 and QLQ-CR29)
- Overall Survival (OS) and PFS for all included patients and for randomized patients
- PFS according to prognostic factors in metastatic CCR patients: baseline CEA, LDH levels and platelet count, & Köhne Score.



Köhne et al. 2002

- Translational ancillary study to assess circulating tumor cells (CTC), circulating free-cell tumor DNA, and microarray gene expression using sequential tumor biopsies to identify potential prognostic/predictive biomarkers
- PFS during second-line treatment

3. STUDY DESIGN

3.1. Evaluation criteria

3.1.1.Main criterion: efficacy

The main criterion is the progression-free survival at 6 months (time from randomization to date of first documented disease progression assessed by CT scan according to RECIST criteria version 1.1, or any cause of death).

3.1.2.Secondary criteria

3.1.2.1. Time to first-line strategy failure

Time to first-line strategy failure defined by time between randomization and disease progression during reintroduced FOLFIRI-cetuximab in both arms, first-line strategy discontinuation (for limiting toxicity or patient choice), or death during first-line strategy

Time to first-line strategy failure including the Phase 1 will be also assessed in the randomized patient population

3.1.2.2. Overall response rate

Overall response rate is defined as the percentage of subjects with a confirmed complete response (CR) or partial response (PR) by investigator assessment as per RECIST 1.1 criteria

Response criteria (RECIST version 1.1)

A maximum of 5 measurable lesions in total (and up to 2 per organ), representative of all involved organs should be identified as target lesions at baseline and measured through the course of study treatment. Target lesions should be selected based on their size and their suitability for accurate repeated measurements. At baseline, the sum of the diameters: longuest diameters (LD) for extra nodal target lesions and short axis diameters (SAD) for nodal lesions will be calculated and reported as the baseline sum LD. This baseline sum LD will be used as the reference by which to characterise the objective tumour response.

All other lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout the study.

Evaluation of target lesions

Complete Response (CR):	Disappearance of all targets extra nodal lesions and the regression of all nodal lesions to < 10 mm SAD.
Partial Response (PR):	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters
Progressive Disease (PD):	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is considered progression.
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study.

Evaluation of non-target lesions

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumour marker level. All lymph nodes must be non pathological in size (< 10 mm short axis)
Non-CR/Non-PD:	Persistence of one or more non-target lesion(s) and/or maintenance of tumour marker level above the normal limits
Progressive Disease (PD):	*Unequivocal progression* of existing non-target lesions and/or appearance of one or more new lesions *

**Although a clear progression of "non target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the review panel (or study chair).*

Evaluation of overall response

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR

PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

3.1.2.3. Progression free survival

Progression Free Survival (PFS) of the randomized study population is defined as the time from the date of randomization to the date of the first documented progression or any cause of death during the study. Progression will be assessed by CT scan according to RECIST criteria version 1.1

•Progression Free Survival (PFS) of the overall included study population is defined as the time from the date of inclusion to the date of the first documented progression or any cause of death during the study. Progression will be assessed by CT scan according to RECIST criteria version 1.1

3.1.2.4. Overall survival

Overall Survival (OS) of the randomized study population is defined as the time from the randomization to the date of documented death

Overall Survival (OS) of the overall included study population is defined as the time from the inclusion to the date of documented death

3.1.2.5. Safety

Safety of the study treatment will be assessed on occurrence of Adverse Events (AEs), intake of concomitant treatments, changes arising, during treatment, in physical examination, vital signs (blood pressure, pulse rate and body temperature), ECG, and clinical laboratory tests (biochemistry, haematology). Safety parameters will be graded based on NCI CTCAE v4.0 classification (May 28th, 2009).

3.1.2.6. Quality of Life

EORTC QLQ-C30 and QLQ-CR29 are questionnaires developed to assess the quality of life of cancer patients, see Appendices 7 and 8

ECOG Performance Status, see Appendix 1

3.1.3.Translational ancillary study (Chapter 11 and appendix 6)

Although some studies have suggested the existence of predictive response factors (tumor size, concomitant chemotherapy) the biological factors determining tumor response are in fact unknown.
The aim of the translational research study will be to identify within the framework of this randomized prospective study, prognostic and predictive biomarkers in advanced CRC patients treated with FOLFIRI + cetuximab as first-line treatment

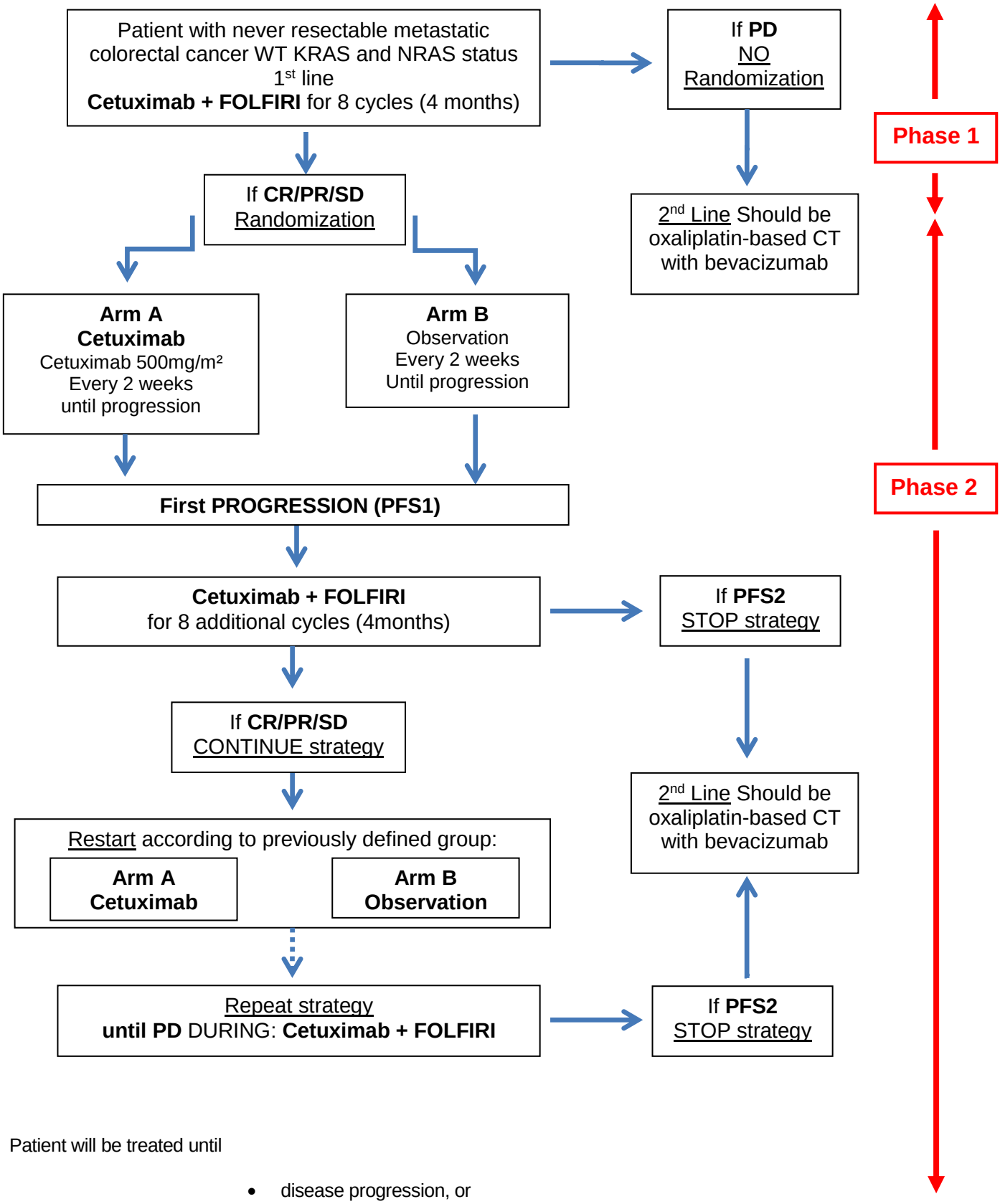
3.2. Methodology/Study Design:

This is national multicentric phase II trial of first-line FOLFIRI plus cetuximab for 8 cycles followed by either single-agent cetuximab as maintenance therapy or observation in patients with wild-type KRAS and NRAS metastatic colorectal cancer

PHASE 1: at inclusion, the entire cohort study will receive biweekly FOLFIRI and cetuximab

PHASE 2: In case of objective response or stable disease after 8 cycles (16 weeks), patients will be randomised into two groups:

1. Group A: patients / cetuximab alone
2. Group B: patients / observation
3. Groups A & B after progression, patients will receive FOLFIRI+cetuximab
4. In the event of response to re-introduction of FOLFIRI + cetuximab, patients will again be followed up as in 1 and 2



Patient will be treated until

- disease progression, or
- limiting toxicity, or
- patient consent withdrawal
- investigator decision

3.3. Inclusion and randomization

After patients have signed the information letter and consent form as well as the forms validating the examinations required for the baseline assessment, eligible patients will be included before first treatment administration of FOLFIRI-cetuximab.
Inclusion will be performed by FAX using the adequate form. An inclusion number will be allocated to the patient.

ICM - Unité de Biostatistique
Monday to Friday from 9 a.m. to 5 p.m.
Fax: +33 (0)4 67 61 37 18
Tel: +33 (0)4 67 61 24 52 / 45 40

At the end of the first 8 courses of FOLFIRI-cetuximab, patients that have not progressed will be randomized.

Randomization will be performed by fax using the randomization form previously used for the inclusion of the patient. The treatment arm will be communicated by return fax.
There will not be a randomization number; the inclusion number will be used to identify the patient for the duration of the trial.

ICM - Unité de Biostatistique
Monday to Friday from 9 a.m. to 5 p.m.
Fax: +33 (0)4 67 61 37 18
Tel: +33 (0)4 67 61 24 52 / 45 40

The inclusion and randomization procedure will be transferred to the investigator during the Site Initiation Visit.

Randomization using a minimization technique will be stratified using the following factors:

- OR (Objective response) vs SD (Stable disease)
- Site
- baseline CEA (<100µg/l vs ≥100µg/l)
- baseline platelet count (<400 000/µl vs ≥400 000/µl
- Köhne Score (1 vs 2 vs 3) (it comprises WBC: <10 000/µl vs ≥10 000/µl, alkaline phosphatase: <300UI/l vs ≥300UI/l, WHO Performance Status: 0 vs ≥1 and number of metastatic sites: 1 vs >1). (Appendix 9)

Treatment must begin within the 7 days following randomization.

3.4. Study work flow

Included patients will participate in the research protocol for the total duration of 4 years
The investigation schedule is defined in the summary table (Paragraph H, synopsis page 10).

3.5. Temporary interruption and definitive termination of the study

The study can be suspended or stopped by the sponsor after meeting with the principal investigator or under the request of the competent authority and/or the Committee for the Protection of Patients (CPP) for the following reasons:

- High frequency and/or unexpected severity of toxicity,
- Insufficient patient enrollment,
- Insufficient quality of data collection.

3.6. Premature trial exit

Premature trial exit will be exceptional and due to the following reasons:

- consent withdrawal,
- lost to follow-up,
- other : exceptional , to be specified by investigator

Patients participating in this research protocol may withdraw their consent and exit the trial at any time without justification irrespective of their reason(s). However, withdrawal of consent does not preclude the patient's right to receive treatment.

4. PATIENT SELECTION

4.1. Inclusion criteria

All the criteria listed below are required for inclusion

1) Histologically confirmed colorectal cancer
2) KRAS and NRAS wild-type genes after analysis of mutation status from the primary tumour or metastasis
3) Non resectable metastatic disease in a curative intent
4) No prior chemotherapy except for fluoropyrimidines with or without oxaliplatin-based adjuvant treatment earlier than 6 months ago from inclusion date
5) Patient presenting with at least one measurable tumour target (≥ 10 mm) according to RECIST criteria, which has never been irradiated
6) Patient with a greater than 3-month life expectancy
7) Performance Status ≤ 2 (WHO)
8) Male or female aged ≥ 18 years.
9) Laboratory requirements
   - Haematology:
     - ✓ Neutrophil count ≥ 1.5 x 10^9/L
     - ✓ Platelet count ≥ 100 x 10^9/L)
     - ✓ Leucocyte count > 1500/mm^3
   - Hepatic Function:
     - ✓ Total bilirubin ≤ 1.5 time the upper normal limit (UNL)
     - ✓ ASAT ≤ 2.5xUNL in absence of liver metastases, or ≤ 5xUNL in presence of liver metastases
     - ✓ ALAT ≤ 2.5xUNL in absence of liver metastases, or ≤ 5xUNL in presence of liver metastases
   - Renal Function
     - ✓ Creatinine clearance (according to Cockroft and Gault formula) ≥ 50 ml/min or blood creatinine level ≤ 1.5x ULN
   - Metabolic Function
     - ✓ Magnesium ≥ lower limit of normal.
     - ✓ Calcium ≥ lower limit of normal

10) Patient who has signed a written informed consent form.

4.2. Non inclusion criteria

One of the following criteria is sufficient for non inclusion:

1) Known and/or symptomatic brain metastases
2) Known allergy to one of treatment components
3) Neurological or psychiatric condition which could interfere with good treatment compliance
4) Patient currently in treatment with any other anti-tumour therapy: chemotherapy or targeted therapy or radiotherapy ≤ 14 days before randomisation
5) Other serious conditions such as: respiratory failure. History of interstitial lung disease e.g. pneumonitis or pulmonary fibrosis or evidence of interstitial lung disease on baseline chest CT scan
6) Clinically significant cardiovascular disease (including myocardial infarction, unstable angina,

symptomatic congestive heart failure, serious uncontrolled cardiac arrhythmia) ≤ 12 months before enrolment or randomisation
7) Concomitant severe infection.
8) History of cancer (except skin cancer other than melanoma or an in situ cervical epithelioma or other solid tumour treated for curative purposes without signs of the condition and with no treatment administered in the 5 years before randomisation.)
9) Patient already included in another clinical trial with an investigational molecule
10) Prior treatment with anti-EGFr antibodies (e.g. panitumumab (Vectibix®) or cetuximab / Erbitux®) or treatment with small EGFr inhibitor molecules (e.g., erlotinib / Tarceva®)
11) Pregnant female, likely to be or currently breast feeding, or planning to become pregnant within 6 months after the end of treatment or absence of effective contraception for males and females of childbearing age during treatment and for 6 months (male or female) after the end of treatment
12) Those deprived of their freedom or under guardianship
13) Impossibility of undergoing trial's medical follow-up for geographical, social or psychological reasons

5. TREATMENTS PROCEDURE

5.1. PHASE 1: At inclusion

Treatment to be started in the entire cohort study (Phase 1): biweekly FOLFIRI and cetuximab as follows:

- Cetuximab: 500 mg/m^2 iv infusion (starting with 120 min for the 1st infusion (infusion rate must not exceed 5mg/min), 90 min for the 2nd (infusion rate must not exceed 10mg/min) and subsequently a minimum of 60 min (infusion rate must not exceed 10mg/min) if infusions are well tolerated) on D1 of each cycle

One hour after the end of the cetuximab perfusion:
- Irinotecan 180 mg/m^2 IV infused over 90 minutes
- Leucovorin 400 mg/m^2 (or 200 mg/m^2 of l-leucovorin) IV infused over 2 hrs (concurrently with irinotecan via separate infusion lines)
- 5-FU 400mg/m^2 IV bolus injection (following LV administration), then 2400 mg/m^2 continuous IV infusion over 46-48 hours.

Cycles will be repeated every 2 weeks

- Systematic preventitive treatment of cetuximab-induced skin toxicity and infusion related reactions in both of the study arms
- Tumour assessment by computed tomography scans will be done within 21 days before inclusion and then repeated every 8 weeks (tumour response according to RECIST)

In case of objective response or stable disease after 8 cycles (16 weeks) ➔ Randomization
Patients who have progressive disease or can not be evaluated after 8 cycles (16 weeks) will not be randomized.

5.2. PHASE 2: Randomization at 16 weeks

Investigational treatment arms:

5.3. Arm A: cetuximab (1 cycle = 2 weeks):

Cetuximab: 500 mg/m², every 2 weeks: 500 mg/m^2 iv infusion (starting with 120 min (infusion rate must not exceed 5mg/min), a minimum of 90 min for the 2nd (infusion rate must not exceed 10mg/min) and subsequently a minimum of 60 min (infusion rate must not exceed 10mg/min) if infusions are well tolerated) on D1 of each cycle.
One cycle consists of 14 days (2 weeks). Patients are eligible for repeated treatment cycles in the absence of disease progression or undue adverse events.

5.4. Arm B: observation

Observation until disease progression

5.5. Arm A and B: Phase 2 after progression

If there is evidence of progression of disease using RECIST criteria or clinical evidence of deterioration, the FOLFIRI plus cetuximab chemotherapy will be reintroduced for a further 8 cycles (16 weeks), starting at the last dosage from Phase 1. (Cetuximab will not be continued if there is unacceptable cetuximab related toxicity).
This therapeutic strategy will be stopped in case of disease progression under FOLFIRI plus cetuximab.
In the absence of disease progression after 8 subsequent cycles of FOLFIRI plus cetuximab, a new cetuximab maintenance (Arm A) / observation period (Arm B) until the next disease progression will be planned.

If any patient during a therapeutic pause is shown to have progressed the patient should resume the protocol therapy (FOLFIRI + cetuximab), unless the clinician feels this is clearly not in the patient's best interests. Patients with chemo-biological sensitive disease may have an unlimited number of 16-week treatments alternating with chemotherapy breaks (with the cetuximab continued in these breaks, if the patient is in Arm A).

When the patient demonstrates resistance to this treatment schedule as evidenced by progressive disease during a period on biochemotherapy (i.e. both the cetuximab + chemotherapy) they should stop protocol treatment and move on to second-line therapy containing oxaliplatin associated with bevacizumab.

6. Administration modalities

6.1. Cetuximab

Cetuximab will be administered by IV infusion on day 1 of each cycle 1 hour prior to the administration of chemotherapy (see Section 6.6.2). One treatment cycle is defined as the 14 day period following the commencement of treatment with cetuximab + FOLFIRI plus additional time, as needed, for the resolution of FOLFIRI-related toxicities. In the event a cycle is delayed beyond 14 days due to chemotherapy-related toxicity, administration of cetuximab alone is recommended. For subjects randomized to receive cetuximab as a maintenance therapy, cetuximab monotherapy should be administered every 14 days (± 3 days).

6.2. Dosage and administration of cetuximab

Cetuximab administration during treatment initiation (combination with FOLFIRI): Cetuximab should be administered at a dose of 500 mg/m² before FOLFIRI chemotherapy. FOLFIRI should be initiated one hour after the end of cetuximab infusion:

First infusion: 500 mg/m² cetuximab (= 100 ml/m² solution ready for use) by IV infusion using infusion pump, gravity drip, or syringe pump,

For the first injection, cetuximab will be infused over a minimum of 2 hours (infusion rate must not exceed 5mg/min)
For the second dose, cetuximab will be infused over a minimum of 1.5 hours (infusion rate must not exceed 10mg/min)
For subsequent doses, the recommended infusion period is over a minimum of 1 hour (infusion rate must not exceed 10mg/min)

Pre-emptive treatment for cetuximab related infusion reaction: Before the first 3 infusions, patients must receive premedication with an antihistamine and a corticosteroid at least 1 hour prior to administration of cetuximab, to reduce the risk of a reaction to the injection, as follows: IV methylprednisolone 120 mg + IV

polaramine 5 mg. This premedication is recommened prior to all subsequent infusions, but may be stopped from the 4th cycle in the absence of an infusion-related allergic type reaction.

Pre-emptive treatment for cetuximab related skin toxicity by systemic antibiotics (tetracycline such as doxycycline 100 mg / day) will be systematically introduce to decrease the frequency and severity of skin toxicity. It is recommended to treat patient throughout the treatment period to reduce the risk of interrupting or delaying cetuximab because of severe skin rash.

Cetuximab should be administered under the supervision of a physician experienced in the administration of cytotoxic drugs.

Close observation is necessary for the duration of infusion of cetuximab and for at least 1 hour after the end of the infusion (either during chemotherapy associated with cetuximab or cetuximab alone

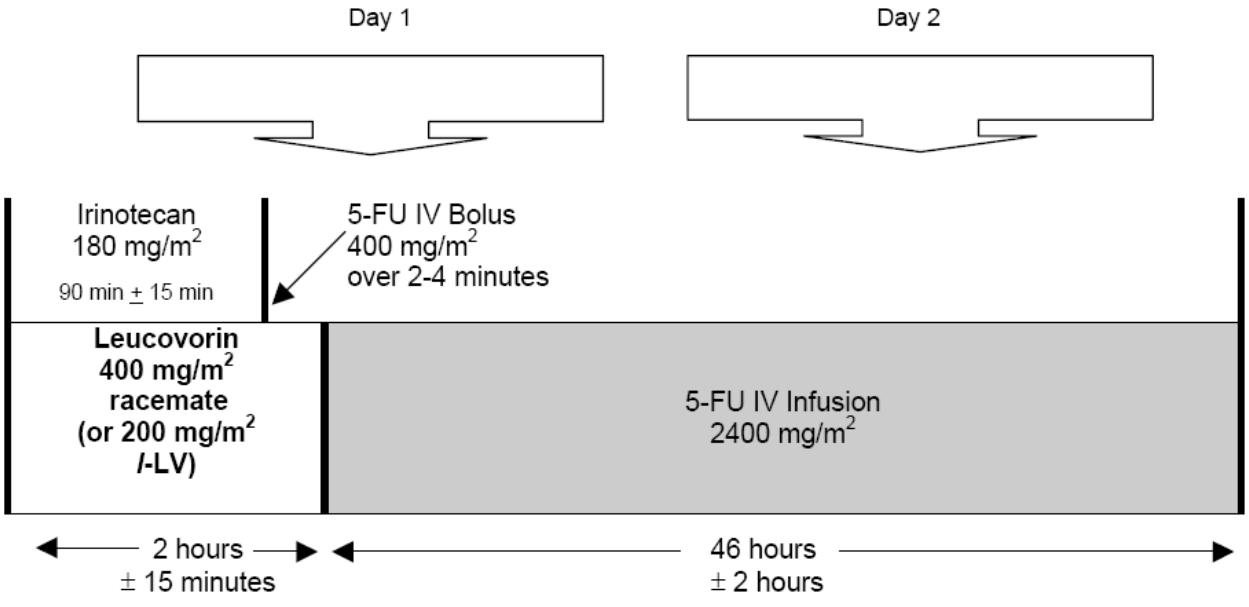
Throughout this time of treatment and monitoring, it is essential to have complete resuscitation equipment nearby.

6.3. Dosage and administration of FOLFIRI

Prior to the administration of FOLFIRI, all subjects should receive antiemetics agents (oral or IV: methylprednisolone, and 5-hydroxtryptamine3 (5-HT3) receptor antagonists),administered before cetuximab. Antiemetic agents should be given on the day of treatment, starting at least 30 minutes prior to administration of irinotecan. Alternative and additional antiemetics may be used, where clinically indicated, at the discretion of the investigator or according to standard institutional or regional practice.

Irinotecan will be administered over 90 minutes ± 15 minutes on day 1 of each cycle.
Leucovorin will be administered over 2 hours ± 15 minutes during the irinotecan infusionbut without mixing, immediately followed by a 5-FU bolus and a 5-FU 46-hour ± 2-hours continuous intravenous infusion.
A new cycle of FOLFIRI may begin only when the absolute neutrophil count is≥ 1300/mm^3, the platelet count is ≥ 90,000/mm^3, FOLFIRI-related diarrhea is fully resolved or has returned to baseline, and all other treatment-related toxicities (except for alopecia) are ≤ grade 1. If this is not the case, the next cycle of chemotherapy will be delayed for up to 3 weeks.

FOLFIRI administration schedule



7. Management of adverse events and dosage adjustments guidelines

7.1. Common Terminolgy Criteria for Adverse Events (CTCAE)

Toxicity will be recorded according to thevCTCAE-NCI v4.0.

- Patients who experience toxicities while on study, dose modification or delay in administration should be performed according to the schedule described below.
- In the case a dose reduction is necessary; the reduced posology (dosage) will be maintained until the end of treatment.
- In case of **recurrent grade ≥3 toxicity** or unacceptable toxicity despite dose reduction, the clinical investigator and the patient may discuss the possibility of stopping the treatment.

Toxicity that has led to discontinuation of treatment but is not related to treatment or progression will not result in permanent discontinuation of treatment. Indeed, a resumption of the treatment will be possible. Treatment-related toxicity may delay the injection until a grade ≤ 1 is restored. The postponement of the treatment will be for a maximum of 28 days (i.e. 2 cycle). Beyond this period the treatment will be definitively stopped.

7.2. Dose adaptation according to cetuximab-induced toxicities

7.2.1.Management of dermatologic toxicity

A proactive and early approach to management of rash is crucial. Rash can be managed by a variety of treatment options to relieve symptoms and improve the rash. Photo-documentation of rashes should be performed. It is recommended to treat patients all along the treatment period to reduce the risk of interrupting investigational treatments because of severe skin rash.

General/Prevention:

- strict sun protection; use of a sunscreen of SPF 15 or higher, preferably containing zinc oxide;
- use of a thick, alcohol-free emollient cream;
- avoid harsh detergents
- Avoid local aggravating factors (friction, trauma, manipulation…)
- antisepsis

Proposal for topical treatment:

- *Emollient twice a day on body surface areas where skin rash occurs (exple: DEXERYL, CICALFATE)*
- *Hydrocortisone cream and lotion (1% or 2.5%) (exple DIPROSONE)*

Systematic preemptive treatment of cetuximab -induced skin toxicity in both arms with Systemic antibiotics such as Doxycycline 50 to 200mg/day during 1 or 2 month (exple: TOLEXINE 100mg/d) [Jatoi A, Rowland K, Sloan JA et al. Tetracycline to prevent epidermal growth factor receptor inhibitor-induced skin rashes: results of a placebo-controlled trial from the North Central Cancer Treatment Group (N03CB). Cancer 2008 Aug 15;113(4):847-53; Scope A, Agero AL, Dusza SW et al. Randomized double-blind trial of prophylactic oral minocycline and topical tazarotene for cetuximab-associated acne-like eruption. J Clin Oncol 2007 Dec 1;25(34):5390-6]

- Antihistamines

Oral prednisone (short term i.e., <14 days treatment) may be added at Investigator's discretion

Table 3: management of dermatologic toxicity

ARM A		**Dermatologic traitement**	**cetuximab**
Grade 0,1		Topical treatment with or without systemic treatment	Performed as planned
Grade 2		Topical treatment and Systemic treatment	Performed as planned
Grade 2 for ≥7consecutive days Grade 3 Patient poor tolerance	1st occurrence	Topical treatment and systemic treatment	Hold infusion until recovery to CTCAE ≤ grade 2. Resume treatment at dose 500mg/m²
	2nd occurrence	Topical treatment and systemic treatment	Hold infusion until recovery to CTCAE ≤ grade 2 or baseline in the individual treatment course Resume treatment at reduced dose 400mg/m²
	3rd occurence	Topical treatment and systemic treatment	Hold infusion until recovery to CTCAE ≤ grade 2 or baseline in the individual treatment course Resume treatment at reduced dose 300mg/m²
	4rd occurence	Topical treatment and systemic treatment	Treatment should be permanently discontinued

7.2.2.Management of allergic / hypersensitivity reaction

In each case of a hypersensitivity reaction, the investigator should institute treatment measures according to the best available medical practice. Based on previous experiencewith cetuximab hypersensitivity reactions, the following treatment guidelines may be applicable:

- **CTCAE grade 1 allergic reaction/hypersensitivity**
  Description: mild transient reaction (transient flushing or rash, drug fever <38°C
  Treatment: decrease the cetuximab infusion rate by 50% and monitor closely for any worsening. The infusion rate may be reduced by 50% again, but stability limits should not be exceeded.

- **CTCAE grade 2 allergic reaction/hypersensitivity**
  Description: flushing, urticaria, dyspnoea, drug fever ≥38°C and/or bronchospasm, promptly responsive to interruption of infusion and symptomatic treatment.
  Treatment:
  1) stop cetuximab infusion
  2) Administer bronchodilators, oxygen, antihistamines etc. as medically indicated
  3) Resume infusion at 50% of previous rate once allergic/hypersensitivity reaction has resolved or decreased to grade 1 in severity, and monitor closely for any worsening. Prolongation of infusion duration should be performed as described for grade 1 reactions.

- **CTCAE grade 3 or 4 allergic reaction/hypersensitivity**
  Description:
  - A grade 3 reaction consists of: symptomatic bronchospasm, requiring parenteral medication(s), with or without urticaria; allergy-related edema/angioedema). Not rapidly responsive to brief interruption of infusion, and/or to symptomatic medication; recurrence of symptoms following initial improvement; hospitalisation required.

- A grade 4 hypersensitivity reaction is a life-threatening event characterized by rapid onset (often within minutes) of any of the following:
    - Airway obstruction/respiratory distress (bronchospasm, stridor, hoarseness, difficulty speaking, etc.)
    - Vascular collapse or shock
    - Cutaneous manifestations (pruritus, urticaria)
    - Angioedema
    - Gastrointestinal manifestations, including dysphagia, cramping, nausea, diarrhea.
- A grade 4 hypersensitivity reaction may be complicated by symptomatic hypotension or oxygen saturation of 70% or less.

Treatment:
1) Stop the cetuximab infusion immediately and disconnect infusion tubing from the patient
2) Administer epinephrine, bronchodilators, antihistamines, glucocorticoids, intravenous fluids, vasopressor agents, oxygen, etc. as medically necessary.

For a CTCAE grade 3 or 4 allergic reaction/hypersensitivity, the patient should not receive further cetuximab treatment.

7.2.3.Management of electrolytes disorder

7.2.3.1. Hypomagnesemia

Cetuximab treatment can compromise renal magnesium retention capacity and lead to persistently low serum magnesium levels. Early symptoms of hypomagnesemia are fatigue, paresthesias and muscle cramps. Magnesium can be administered either orally in an oxide, chloride or gluconate form or parenterally as a sulphate salt.

Suggested guidelines for management of hypomagnesemia are as follows (R09-1587):

- Grade 1 hypomagnesemia (Mg < LLN-1.2 mg/dl), magnesium chloride starting at 2 tablets PO three times a day, titrating up to 4 tablets PO three times a day as needed.
- Investigators may also consider weekly magnesium monitoring without replacement for grade 1 hypomagnesemia in asymptomatic patients without cardiac history or cardiac risks.
- Grade 2 hypomagnesemia (Mg < 1.2-0.9 mg/dl) weekly intravenous replacement with magnesium sulfate 4 g for patients with magnesium levels of 0.9 to 1.0 mg/dL.
- Grade 3/4 hypomagnesemia (Mg < 0.9-0.7, Mg < 0.7): magnesium sulfate 6 to 10 g IV twice weekly, dependent on the patient. An initial strategy of IV replacement and every-other-day serum magnesium monitoring is helpful to guide the frequency of replacement until a steady state is reached. In a patient with normal renal function start amiloride 5 mg PO daily and titrate up to 10 mg PO daily.

7.2.3.2. Hypocalcemia

Secondary hypocalcemia is associated with hypomagnesemia.
Correction of the hypomagnesemia usually results in normalization of serum calcium levels.

7.2.4.Management of Pulmonary toxicity

For patients who present acute pulmonary symptoms or worsening of preexisting pulmonary symptoms, investigational treatments should be discontinued until symptoms resolve.
Search for ILD
No retreatment if evidence of ILD

Interstitial pneumonitis

Interstitial lung disease (ILD) events have been reported in patients treated with gefitinib. At present, no increased risk of developing interstitial lung disease was observed with cetuximab. However, as a precaution, patients should have a CTscan before the start of cetuximab.

If, a patient presents respiratory symptoms, the investigator will conduct pulmonary function tests and diagnostic work specializing in search of pulmonary fibrosis or underlying interstitial lung disease.
In addition, patients should be regularly examined for signs of lung during the study.

7.2.5.Management of other toxicities

For Any other toxicity Grade ≥3 (except alopecia):

- Cetuximab
    - Hold injection until recovery to ≤ grade 1 for cetuximab-related CTCAE
    - Resume treatment at same dose of 500mg/m² (1st occurrence), 400mg/m² (2nd occurrence), 300mg/m² (3rd occurrence), treatment should be permanently discontinued (4th occurrence)

7.3. Dose adaptation according to FOLFIRI-induced toxicities

7.3.1.Hematologic toxicity

Before reducing doses of chemotherapy, G-CSF as secondary prophylaxis will be use as soon as there is evidence of either febrile neutropenia or grade 4 neutropenia or neutropenia has not recovered on day 15 and by delaying the cycle, with a prescription for 263 mg/d from D5 to D12. The administration of GCSF will be maintained for subsequent cycles

	DELAY CYCLE	**REDUCTION OF DOSE**	
		Irinotecan (CPT-11)	**LV5FU2**
ANC ≥ 1,5 x 10^9 /l And PTL ≥ 75x10^9 /l	No cycle delay	No reduction dose	
ANC< 1,5 x 10^9/l	Delaying treatment until ANC ≥ 1.3 x 10^9/l (D22 or D29 up if necessary). In case of no recovery at D29 traitement will be definitlively interrupted	At the first occurrence: no reduction dose At the second occurrence: reduction of dose to 150 mg/m² At the third occurrence: **GCSF**	At the first occurrence : reduce the dose of bolus of 50% At the second occurrence: remove the bolus at D1
PTL < 75x10^9 /l	Delayed until recovery (PTL ≥80x10^9/l). In case of no recovery at D29, traitement will be stopped	At the first occurrence no reduction dose At the second occurrence reduction of dose to 150 mg/m² At the third occurrence: reduction of dose to 120 mg/m²	At the first occurrence : reduce the dose of bolus of 50% At the second occurrence: remove the bolus at D1

(*)if no recovery after 2 delays treatment, stopping treatment unless obvious clinical benefit: the case will be discussed with the study coordinator and sponsor

7.3.2.Gastro intestinal toxicity

7.3.2.1. Management of diarrhea

Close monitoring and proactive management of diarrhea is essential for successful treatment of patients with irinotecan. Early and appropriate intervention can prevent the development of more severe diarrhea. In most cases, loperamide controls diarrhea caused by irinotecan. Loperamide should be available at the start of

therapy and kept with the patient at all times; it is therefore advisable that patients be given a prescription at the time of initiating investigational treatment.

If any diarrhea is experienced:

- Two 2 mg loperamide tablets should be taken immediately, followed by one 2 mg tablet with every loose bowel movement, up to a maximum daily dose of 10 tablets (20 mg) Patients should avoid lactose-containing products or any foods known to aggravate diarrhea
- Oral hydratation is essential regardless of severity. Appropriate rehydration (1.5 l/m^2/day plus equivalent of actual fluid loss) has to be ensured. Patients with significant electrolyte changes should receive intraveinous rehydration and electrolyte replacement.
- Patients should be evaluated frequently until resolution of diarrhea

EVENTS	DOSE REDUCTION FOR NEXT CYCLES
-Diarrhea grade **3-4** - Diarrhea and associated fever and/or neutropenia grade 3-4	At the first occurrence : dose reduction of irinotecan to 150 mg/m^2 and 5FU bolus should be discontnued At the second occurrence : dose reduction of irinotecan to 150 mg/m^2 and dose reduction of continuous infusion 5FU at 75% At the third occurrence : **irinotecan will be discontinued**
resistant diarrhea (> 48 h) despite high doses of loperamide	No dose reduction of irinotecan or 5-FU after recovery unless grade 3-4 diarrhea, or diarrhea + fever and / or grade 3-4 neutropenia

7.3.3."Hand-foot": Syndrome

In case of grade 3-4 toxicity, a dose reduction of 25% of continuous infusion 5-FU will be applied for next cycles.

7.3.4.Cardiac toxicities :

The treatment will be stopped permanantly.
In case of angina or myocardial infarction, all treatment should be stopped.

7.3.5.Livers discorders/Increased bilirubin

EVENTS	DOSE REDUCTION FOR NEXT CYCLE
35 µmol/l < Bilirubin ≤ 50 µmol/l OR 21 mg/l< Bilirubin ≤ 30 mg/l	Dose reduction of IRINOTECAN at 150 mg/m²2
Bilirubin > 50 µmol/l	Irinotecan must be discontinued

7.3.6.Other toxicities:

Other toxicities≥ any other toxicity grade 2, except for alopecia and anemia, may justify a reduction in dosage if medically indicated: reduction of irinotecan to 150 mg/m² and / or 25% reduction of 5-FU depending on the type of toxicity

7.4. Concomitant therapy

St. John's wort (Hypericum perforatum) decreases plasma levels of SN-38 (active metabolite of irinotecan). Therefore, St. John's wort should not be administered with irinotecan.

Particular care is required in patients receiving concomitant medications known to inhibit (e.g. ketoconazole) or induce (e.g. rifampin, carbamazepine, phenobarbital, or phenytoin) cytochrome CYP450 3A4 metabolism. Coadministration of irinotecan with an inducer or inhibitor of this metabolic pathway may alter the metabolism of irinotecan and should be avoided.

Concomitant administration of cytochrome CYP3A-inducing anti-seizure drugs (such as carbamazepine, phenobarbital, or phenytoin) resulted in decreased exposure to irinotecan, SN-38, and SN38 glucuronide and reduced their pharmacodynamic effects.

Subjects should receive full supportive care during the study, including transfusion of blood and blood products, and treatment with antibiotics, anti-emetics, antidiarrheals, and analgesics, as appropriate.

All medications and non-drug therapies (including physical therapy and blood transfusions) taken within 14 days prior to starting study treatment and during the study duration, until last study drug dose, should be reported on the concomitant treatment form of the study CRF.

The investigator should instruct the patient to notify the study site about any new medications (including over-the-counter drugs and herbal/alternative medications (St. John's wort) he/she takes after the start of study treatment. Patients must be instructed not to take any additional medications (including over-the-counter products and herbal/alternative medications) during the trial without prior consultation with the investigator.

7.5. Proscribed therapy

Prohibited treatments include:

- Subjects should not receive other anti-cancer non-drug therapies: radiation, or tumor embolization within 2 weeks prior to the first dose of study drugs and while on study treatment.
- Yellow fever vaccine
- Phenytoin prescribed as prophylactic anticonvulsive agent
- Any investigational treatment related or not related to colorectal cancer, including radiotherapy

8. PHARMACY GUIDE

8.1. Supply, Packaging, Labeling, Storage conditions

The cetuximab (Erbitux®), the 5-FU, leucovorin and irinotecan are not supplied by the sponsor during the treatment with FOLFIRI and cetuximab (since this prescription corresponds to the market authorization of these products). The cetuximab will be provided by the sponsor during the second phase of treatment, during the maintenance period with cetuximab, as a monotherapy, for those patients randomized in the Arm A.

8.2. Storage conditions:

Please refer to the most current SPC.

9. BASELINE ASSESSMENT AND FOLLOW-UP

A table summarizing patient monitoring and evaluation schedule from the date of randomization till the end of the study can be found in section H of the protocol synopsis.
Prior to any study activities, the patient will be asked to read and sign an informed consent form that has been approved by an Independent Ethics Committee/Institutional Review Board (IEC/IRB) and which

complies with regulatory requirements. Patients will be given adequate time to consider any information concerning the study given to them by the investigator. As part of the informed consent procedure, patients will be given the opportunity to ask the investigator any question regarding potential risks and benefits of a participation in the study

9.1. Visit 1 – Screening (within 28 days before start of treatment)

Prior to any study activities, the patient will be asked to read and sign an informed consent form that has been approved by an Independent Ethics Committee/Institutional Review Board (IEC/IRB) and which complies with regulatory requirements. Patients will be given adequate time to consider any information concerning the study given to them by the investigator. As part of the informed consent procedure, patients will be given the opportunity to ask the investigator any question regarding potential risks and benefits of a participation in the study.

The following assessments and investigations will be conducted during Visit 1:

- Check eligibility of patient including the absence of any mutations of the KRAS and NRAS genes. The tumour blocks used for the tumour diagnosis will systematically be centralized to verify and if necessary complete the analysis of these mutations.
- Demographics data
- Colorectal cancer history and diagnosis
- Relevant medical history and procedure history

9.2. Baseline assessment

Eligible patients with informed signed consent will undergo a clinical examination and a biological evaluation within the 7 days preceding initial treatment with FOLFIRI+Cetuximab

- **Clinical examination**
  - Complete clinical examination including vital signs with neurological assessement: weight, height, pulse, blood pressure, WHO performance status, comorbidities, current treatments and saturation **SvO_2**.
- **Paraclinical examinations** (to be performed within maximum 30 days before randomization)
  - Checking the electrocardiogram
  - Thoraco-abdomino-pelvic CT scan.
- **Biological tests**
  - Hemogram with platelets,
  - Ionogram test ,calcemia, magnesemia,
  - Renal evaluation (creatininemia,, creatinine clearance, urea)
  - Hepatic evaluation (Alkalin phosphatases, total bilirubin, free and conjugated, GGT, AST and ALT)
  - CEA,
  - LDH
  - Pregnancy test for fertile women without contraception
- **QLQ C30 and QLQ- CR29 (Appendix 7)**
- **Translational research (Appendix 6) :**
  - **Blood samples**: 7,5mL (in a Cell Save tube) and 10ml (EDTA)
  - **Biopsies (optional)**: Fixed and frozen tumor and healthy tissue biopsies

9.3. Evaluation during the 16 weeks-period preceeding randomization

9.3.1.Every two weeks (14 days) (before each treatment with FOLFIRI-cetuximab) :

Patients treated with cetuximab will be evaluated with a clinical examination before each administration to assess toxicities and decide whether the treatment can be continued.

- **Clinical examination**
  - Clinical examination including weight and vital signs
  - WHO performance status
  - Evaluation of tolerance during the inter-cycle interval
  - Checking the recovery from toxicities to baseline
  - Checking for concomitant therapy

- **Biological tests**
  - Hemogram with platelets,
  - Ionogram test (calcemia and magnesemia)
  - Hepatic test (Alkalin phosphatases, total bilirubin, free and conjugated, GGT,AST and ALT).

9.3.2.Every eight weeks: (tumor evaluation):

- **Biological tests**
  - LDH (every 8 weeks)
  - CEA (every 8 weeks)
  -
- **QLQ C30 and QLQ- CR29 (every 8 weeks)**

- **Paraclinical examinations (every 8 weeks)**
  Thoracic-abdominal-pelvic CT scan

However, in case of intolerance, additional consultations/visits may be scheduled.

All examinations revealing toxicity related to the treatment must be repeated periodically until the toxicity has been resolved (or until it is deemed irreversible).

9.4. Evaluation at Randomization

- **QLQ C30 and QLQ- CR29**

- **Paraclinical examinations**
  Thoracic-abdominal-pelvic CT scan

- **Translational research (Appendix 6) :**
  - **Blood samples**: 7,5mL in a Cell Save tube and 10ml in an EDTA tube. These blood samples are also applicable to patients that are not eligible for randomization.
  - **Tumor biopsy**: In the case of a progressive disease during the FOLFIRI – cetuximab phase, second optional biopsy, fixed and frozen tumor tissue.

9.5. Evaluations after randomisation (performed to verify the control of the disease after the initial 16 week treatment period with FOLFIRI and cetuximab)

9.5.1.Evaluation during the maintenance period and the therapeutic pause (patients in both Arm A and Arm B)

9.5.1.1. Every two weeks (14 days)

- Cetuximab alone every two weeks administration in Arm A
- Observation in Arm B

Patients will be evaluated every two weeks in both arm:

- **Clinical examination**
  - Clinical examination including weight and vital signs
  - WHO performance status

- Evaluation of tolerance during the inter-cycle interval
- Checking the recovery from toxicities to baseline
- Checking for concomitant therapy

- **Biological tests**
  - Hemogram with platelets,
  - Ionogram test (calcemia, magnesemia)

- **Translational research (Appendix 6)**
  7,5ml (in a Cell Save tube) and 10ml (EDTA) to **be collected 1 month after randomization**

9.5.1.2. Evaluation every 8 weeks until progression

- **Biological tests**
  - CEA,
  - LDH

- **QLQ C30 and QLQ- CR29**

- **Paraclinical examinations**
  - Thoracic-abdominal-pelvic CT scan

However, in case of intolerance, additional consultations/visits may be scheduled.

All examinations revealing toxicity related to the treatment must be repeated periodically until the toxicity has been resolved (or until it is deemed irreversible).

9.6. Evaluation at the first progression (during monotherapy or therapeutic pause phase)

- **QLQ C30 and QLQ CR29**

- **Paraclinical examinations**
  - Thoracic-abdominal-pelvic CT scan

- **Translational research (Appendix 6)**
  Blood samples: 7,5ml (in a Cell Save tube) and 10ml (EDTA)

9.7. Evaluation during the reinitiation of FOLFIRI – cetuximab treatment following a progression during monotherapy or therapeutic pause

9.7.1.Every two weeks (before each treatment by FOLFIRI – cetuximab)

Patients treated with cetuximab will be evaluated by clinical examination prior to each administration to assess toxicities and to decide whether treatment can be continued.

- **Clinical examination**
  - Clinical examination including weight and vital signs
  - WHO performance status
  - Evaluation of tolerance during the inter-cycle interval
  - Checking the recovery from toxicities to baseline
  - Checking for concomitant therapy

- **Biological tests**
  - Hemogram with platelets,
  - Ionogram test ,calcemia, magnesemia,
  - Renal evaluation (creatininemia,, creatinine clearance, urea)
  - Hepatic evaluation (Alkalin phosphatases, total bilirubin, free and conjugated, GGT, AST and ALT)

9.7.2.Every 8 weeks (tumour evaluation)

- **Biological tests**
  - CEA,
  - LDH
- **QLQ C30 and QLQ CR29**
- **Paraclinical examinations**
  - Thoracic-abdominal-pelvic CT scan

9.8. Evaluation at the second progression during FOLFIRI – cetuximab treatment

- **QLQ C30 and QLQ CR29**
- **Paraclinical examinations**
  - Thoracic-abdominal-pelvic CT scan
- **Translational research (Appendix 6)**
  Tumor biopsy (optionnelle): In the case of a progressive disease during the FOLFIRI – cetuximab phase, second optional biopsy, fixed and frozen tumor tissue.

9.9. Follow-up after failure to FOLFIRI-cetuximab :

9.9.1.Follow-up every 8 weeks during second-line of treatment (after PFS2)

The recommended second-line treatment is oxaliplatin-containing chemotherapy combined with bevacizumab

- Type and schedule of second-line treatment
- Tumour response according RECIST by CT scan or MRI
- Vital status

9.9.2.Follow-up every 8 weeks under subsequent treatment lines

- Type and schedule of subsequent treatment lines
- Vital status

10. SAFETY EVALUATION

10.1. Adverse Events

10.1.1. General definition

An adverse event is defined as any medical event, or any event requiring clinical investigation, occurring during treatment, whether or not it is attributable to the study drugs (especially: abnormal biological exams, symptoms, new or impaired concomitant diseases…). Any variation of the studied disease, excepted for serious impairment, is not considered an adverse event. Any event occurring during the trial (from signature to one month after last study drug intake) must be reported in the case report form.

As far as possible, each AE should be evaluated to determine:

1. The severity grade (CTCAE grade 1-5)
2. Its relationship to each study drug (suspected/not suspected)
   The investigator must do his/her best to explain each adverse event and establish, when it exists, the connection with each trial's product.
   Causality will be established for each product as follows:

- no, it is not related;
- yes, there is a reasonable possibility of causality according to the following criteria:
  - the pharmacology of the product is known,
  - the effects are of similar nature compared to already known effects reported for this product or other products of the same family or category of compound,

adverse event already reported in the literature for similar products and being considered as related to the study product

  - adverse event tightly related to the treatment period (between the beginning of the administration – the drug challenge period – and the end of administration – dechallenge period) or positive rechallenge.

3. Its duration (start and end dates or if continuing at final exam)
4. Action taken (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication taken, non-drug therapy given; hospitalization/prolonged hospitalization)
5. Whether it is serious, where a serious adverse event (SAE) is defined in section 8.1.

10.1.2. Adverse events follow-up:

All AEs, serious and non-serious, occurring during the course of the clinical trial (i.e., from signing the informed consent onwards until 28 days after end of treatment), regardless of relatedness or listedness, will be collected, documented and reported to the sponsor by the investigator on the appropriate reporting forms. Serious and non-serious AEs occurring later than 28 days after last administration of study medication will only be reported in case they are considered drug-related or trial related. All AEs, including those persisting after end of study medication must be followed up until they have resolved or have been sufficiently characterised unless the sponsor and the investigator agree to not further pursue them.

10.2. Serious Adverse Events

10.2.1. General definition

A serious adverse event is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,
- requires in patient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability / incapacity
- induces a congenital anomaly / birth defect or abortion,
- is medically relevant.

The terms disability and incapacity match with all physical/psychological temporary or permanent handicap, clinically significant with consequences on the physical activities and/or the quality of life of the patient.

Any clinical event or laboratory result considered serious by the investigator and/or the sponsor and not corresponding to the severity criteria defined above is considered medically significant. They may put the patient at risk and require medical intervention to prevent an outcome corresponding to one of the severity criteria mentioned above (overdose, second cancers, intensive treatment in the emergency room may be considered medically significant).

Is not considered as Serious Adverse Event:

- All Hospitalization :
  - ✓ Less than 24 hours*,
  - ✓ Hospitalisation already scheduled before the start of the trial,
  - ✓ Provided by the research Protocol
  - ✓ Hospitalization occurring in the context of tumour progression of disease under trial,

- Progression of disease under trial,
- Clinical events related to progression of disease under trial.

Only those disease progressions that result in death and occur during the notification period defined by the protocol should be notified as SAEs.

**Hospitalizations of less than 24 hours, concerning care, procedures, examinations or any investigation carried out on ambulatory or in a day hospital without associated severity criteria.*

10.2.2. Definition of suspected unexpected serious adverse event (SUSAR)

Is defined as any serious adverse reaction, the nature, severity or outcome is not consistent with the information contained in the reference document of the expected/unexpected assessment (summary of product characteristics or investigator brochure).
The reference document for the assessment of expected/unexpected in this study will be the cetuximab SmPC.

10.2.3. Definition of the new fact

A new fact is defined as any fact relevant to the research or to the drug under investigation and likely to affect the safety of the persons under investigation, which leads the sponsor and the investigator to take appropriate urgent safety measures.

10.2.4. Severy criterion

Severy 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 5). The intensity of adverse events not listed in this classification will be assessed according to the following qualifiers:

- **Grade 1**: **Mild**; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2**: **Moderate**, minimal local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
- **Grade 3**: **Severe** or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
- **Grade 4**: Life-threatening consequences; urgent intervention indicated.
- **Grade 5**: **Death** related to the event.

10.2.5. Notification of serious adverse events

The investigator must immediately and no later than 24 hours following knowledge of the event, notifies the R&D UNICANCER pharmacovigilance unit of any SAE or any new event defined hereabove, whether or not related to the research, which occurs during the 'trial reporting period'. This reporting period starts at the date of the signature of the informed consent form, covers an period of 30 days after the last administration into two groups.
Any later SAE, i.e. occurring after a period of 30 days, which is considered to be related to the experimental treatment(s) or to the research (other treatment used, diagnostic procedures and examinations carried out during the research) must be reported without any limitation in terms of deadline.

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Pharmacovigilance unit, France
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e-mail: pv-rd@unicancer.fr

Second cancer must be reported to the R&D UNICANCER pharmacovigilance unit without any limitation in terms of deadline.

Requests for clarification and / or additional information may be sent to the investigator by the R&D UNICANCER pharmacovigilance unit or CRA sponsor of the trial to document and treat the case.

For each event, the investigator will report:

- The patient identification,
- The event's description, as clearly as possible and in accordance with the medical terminology,
- The intensity,
- The date of the event's onset and recovery,
- The seriousness criteria,
- The measures undertaken and necessity to use corrective treatments,
- If the protocol treatment was interrupted,
- The outcome. The event will be followed until remission or recovery of the baseline status or stabilization of possible sequelas,
- The relationship to the study schedule or to a protocol procedure (e.g. treatment schema, additional examinations specifically requested by the protocol, etc.),
- The relationship to the study drugs, to the treated pathology, to another concomitant pathology, or another treatment,

Whenever possible, the investigator should also provide:

- A copy of the hospitalization or prolonged hospitalization report
- A copy of the autopsy report,
- A copy of all complementary examinations results, including the relevant negative results (with normal laboratory values).
- Any other document that is relevant in the investigator's opinion.

All these documents must be made anonymous. More information might be requested by the Safety Office or the study CRA.

10.2.6. SAE follow-up

The investigator is responsible for the appropriate medical follow-up of the patients until the recovery, the stabilization or the death of the patient. **If required, follow-up could be maintained beyond the end of the protocol.** The investigator provides complementary information to the R&D UNICANCER Safety Office using a SAE declaration form (ticking the box: Follow-up # **X** will specify that it is not an initial report) within 48 hours of its obtention. The last follow-up form is sent once recovery or stabilization is observed. The investigator keeps all the documents regarding the SAE in order to answer further information demands from the R&D UNICANCER Safety Office.

10.2.7. Pregnancies

The occurrence of pregnancy is not considered as an SAE, however any pregnancy must be reported with the same modalities as an SAE, using a Pregnancy Notification Form during the treatment period or within 30 days after last trial treatment administration. Pregnancy will be subject to special follow-up until its end. **Any anomaly detected in the foetus or child, any elective termination of a pregnancy for medical reasons or spontaneous abortion will be reported as an SAE as well, using the same procedure as an SAE, and must be submitted in the same manner as described in Section 10.1.5.**

11. Translational study (Appendix 6)

Although some studies have suggested the existence of predictive response factors (tumor size, concomitant chemotherapy) the biological factors determining tumor response are in fact unknown.
The aim of the biological translational research study is will be to identify within the framework of this randomized prospective study, using genomics, the biological factors prognostic and predictive biomarkers of the tumor response and the toxicity of evaluated treatmentin advanced CRC patients treated with FOLFIRI + cetuximab as first-line treatment.

Circulating biomarkers

1. Circulating tumor cells CTC)

For chemotherapy management, some reports have suggested that variations in CTC counts may be associated with treatment response [Aquino A, J Chemother 2002]. For this application, the cytological CellSearch® technique has achieved very strong evidence, with several studies published on metastatic colorectal cancers. Based on the study reported by Cohen et al. [105], the CellSearch® system gained, in 2007, FDA approval as an aid to monitor metastatic colorectal-cancer patients. This study reported the strong and independent prognostic impact of CTC-positivity (≥3 CTC/7.5 ml) at baseline, but also of early CTC changes.

2. Circulating tumor DNA

Cancer is characterized by multiple somatic genetic and epigenetic alterations that could be useful as molecular markers for detecting tumor DNA in different bodily fluids. Advances in polymerase chain reaction (PCR)-based technology now allow the detection and quantification of extremely small amounts of tumor-derived circulating free DNA in patients. According to several studies aimed at assessing the clinical and biological significance of tumor-derived circulating free DNA in CRC patients, tumor-derived circulating free DNA could serve as a marker for the diagnosis, prognosis and early detection of recurrence, thereby significantly improving the monitoring of CRC patients [Lecomte T GCB 2010]. Various types of DNA alterations described in colorectal cancer have been detected in the circulating free DNA of patients with colorectal cancer. These alterations include KRAS2, APC and TP53 mutations, DNA hypermethylation, microsatellite instability (MSI) and loss of heterozygosity (LOH). Today, the main limitation to the noninvasive detection of circulating tumor DNA is the lack of sensitivity of mutation detection methods currently used in clinical practice. Indeed, when conventional methods have sensitivity thresholds in the range of 0.1-1%, mutant tumor DNA represents a very small fraction of total circulating DNA (often less than 0.01% in the case of early cancers). However, recent works by our laboratory and others have recently demonstrated that droplet-based digital PCR procedures could constitute a pertinent approach to screen specific genetic alterations and to detect the presence of cftDNA in plasma of patients with both a high sensitivity and specificity. This technique was validated by demonstrating the ability to quantitatively and accurately detect up to 1/200,000 mutant KRAS in wild-type KRAS (0.0005%) in biological samples of patients with colorectal cancer. In addition, the ability to detect multiple biomarkers in parallel has also been demonstrated (Pekin et al., 2011; Zhong et al., 2011). Moreover in colorectal cancer, our laboratory has demonstrated the prognostic value of such alterations and showed that the presence of cftDNA in plasma can be used to identify patients with high risk of recurrence (Lecomte et al., 2010; Lecomte et al., 2002; Coulet et al., 2000).

The objective of this translational research study will be:

1/ To assess the prognostic and predictive value of circulating CTC and free tumor DNA
We hypothesized that CTC counts and free tumor DNA detection could serve as prognostic and predictive biomarkers (prediction of response and/or early progression).
CTC absolute values and cell-free tumor DNA quantification at each time point will be analyzed according to tumor response and PFS.
We plan to analyze the patient outcome according to threshold value of 3 free CTCs per 7.5 ml (two groups : > 3 CTC/7.5 ml versus < 3 CTC/7.5ml) according to previous published data on CTC in advanced colorectal cancer). We assume that 30% of the patients will be find to have a CTC count above 3/7.5 ml , according to previous data (Tol J et al. Ann Oncol 2010; 21:1006-12)
The mean concentration of free circulating DNA measured in plasma using quantitative PCR assay is around 200ng/ml in patient with cancer and 4ng/ml in healthy subject.

2/ To determine and compare the sensitivity of CTC and cell-free tumor DNA detection in patients with advanced CRC

3/ To determine and compare the characterization of tumor-associated molecular alterations in the circulating free tumor DNA and in the tumor

For this purpose, circulating tumor cells (CTC) and cell-free tumor DNA quantification in blood samples will be performed at 4 time points:

1/ Baseline: before the initiation of chemotherapy with FOLFIRI plus cetuximab in all patients

2/ After 4 months of FOLFIRI plus cetuximab in all patients (at randomization, just before maintenance therapy or observation)
3/ 1 month after randomization in each arm (after one month of maintenance therapy or observation)
4/ At progression in each arm

Tumor biomarkers (Optional)

Patients who agree to participate in this biologic study using biospecimens will be given a **second letter of information** by the clinical investigator and asked to **sign a second consent form**.

A genomic microarray analysis on frozen tissue samples will be performed to build a gene expression signature predictive of response and/or resistance to the combination of FOLFIRI plus cetuximab. The objective of this analysis will be to identify the activation of molecular pathways involved in tumor response and acquired resistance to cetuximab and FOLFIRI detected in tumor samples before treatment and during progression on FOLFIRI-cetuximab.

Sequential fixed and frozen biopsies consisting of one of the tumor and normal tissue before treatment and then a tumor biopsy upon progression on FOLFIRI-cetuximab **(including patients not randomized for progression on FOLFIRI-cetuximab)** will be taken to perform the following analyses:

- expression of EGFR downstream signaling phosphoproteins and PI3K/AKT pathways in the tumor
- gene expression profiling using a whole genome 44K oligonucleotide array

The biopsy or puncture in the tumor area will be performed according to local recommendations. When the biopsy is performed, two samples are collected, one sample is frozen in liquid nitrogen, without delay, at the place where the biopsy is performed and kept under the same conditions. The second sample will be collected in a formalin fixative with a fixation time of 30 minutes (maximum 1 hour). The fixed samples will be stored at 4°C after inclusion in paraffin. The collection procedures may be modified according to the expertise acquired over time and to improve the quality of the analyses. If a surgical procedure is scheduled, these samples can also be taken at that time.

At the same time a biopsy of the normal tissue before treatment will also be performed following the same procedure as above.
The objective is to analyze the biological transformations that occur over time and that are at the origin of a resistance to the study treatment. The objective of this biological research is therefore to comparatively analyze samples before and after treatment (sequential) in order to identify the activation of molecular pathways involved in the response and acquired resistance of the tumor to treatment.

Patients who agree to participate in the tumor biomarker biology study will be given a **second letter of information** by the clinical investigator and will be asked to **sign a second consent form**.

12. STATISTICAL CONSIDERATIONS

12.1. Sample size calculation

This sample size calculation is based on the hypothesis for the experimental arm only.

- 45%-50% patients will present with a KRAS and/or NRAS mutation at initial screening who will therefore not be able to be enrolled in the study, only RAS wild type patients will be enrolled
- Median first-line PFS of patients with KRAS wild type tumours treated with chemotherapy combined with anti-EGFR monoclonal antibodies is about 9 months according to several recent phase III trials.
- Study data on wild KRAS patients, show that about 20% patients will have progressive disease after 4 months of FOLFIRI + cetuximab. We can estimate that the median first-line PFS KRAS patients after the start of treatment would reach 10 months (= 6 months after randomization in the present study, giving a 6 month-PFS rate of 50% after start of maintenance treatment)
- results of COIN B trial in wild KRAS patients showed that first-line PFS médiane pour la première ligne, calculé à partir de la 12ème semaine (after 3 months of FOLFOX+cetuximab) is about 9 6 months dans

le groupe de traitement in the intermittent cetuximab arm (treatment break until progression). The 3-months shorter PFS is the intermittent cetuximab arm is partially compensated by reintroduction of the combination treatment at progression (failure-free survival: 12 versus 14 months).

- La population de cette étude, est désormais restreinte aux patients RAS sauvages avec une SSP médiane d'environ 2 mois de plus que chez les patients KRAS sauvages (selon les résultats mis à jour en 2014 des études FIRE3 et CALGB ; dans cette étude, 8 mois après la randomisation). Le taux de SSP à 6 mois après la randomisation est donc estimé à 60%.

- The sample size is based on the Fleming single stage design (target one-sided alpha=5%, actual alpha=7.8%, target beta=20%, actual beta=14.3%). It will be concluded that cetuximab alone is effective if the 6 month-PFS rate in arm (A) is higher than or equal to 55% and to conclude it is ineffective if the 6 month-PFS rate is lower than or equal to 40%. Sixty seven patients have to be included in the experimental arm (A), and **a total of 134 evaluable randomized patients** are required.
  [Fleming TR. One sample multiple testing procedure for phase II trials. Biometrics 1982; 38:143-151]

  It should be noted that the alpha level is set at 5% (one-sided), the risk of concluding efficacy ($p > p0$) when there is no actual efficacy ($p \leq p0$), and the beta level is set at 20%, the risk of concluding an absence of efficacy ($p < p1$) when there is actually noteworthy efficacy ($p \geq p1$).

  Cetuximab alone arm (A): -if less than 34 patients (out of the 67) are alive without progressive disease at 6 months after randomization, the conclusion will be that cetuximab alone is ineffective. -If 20 or more patients (out of the 54) are alive without progressive disease at 6 months after randomization, the conclusion will be that cetuximab alone is effective.
  Observation arm (B): Patients receiving no treatment constitute an internal control group to validate the hypothesis of a 6 month-PFS of 40%. The 95% confidence interval (CI) of the 6 month-PFS rate will be calculated. If 40% is included in the 95% CI, the conclusion of the study will be interpreted according to the Fleming' decision rule. If 30% is not included in the 90% CI, the conclusion of the study will be interpreted as follow:

The 6 month-PFS rate will be estimatyed after a follow-up of 6 months for all patients.

Group B 95%CI of the 6 month-PFS rate	**Group A conclusion**	
	Cetuximab alone effective	**Cetuximab alone ineffective**
40% < 95%CI lower limit	Results to be discussed	Fleming' Conclusion
40% included in the 95%CI	Fleming' Conclusion	Fleming' Conclusion
40% > 95%CI upper limit	Fleming' Conclusion	Results to be discussed

- Considering that a maximum of 30% patients will have progressive disease after 4 months of FOLFIRI + cetuximab, we have to include 61 more patients. **Therefore a total of 195 patients have to be included in the trial.**

No formal statistical comparison will be made.

12.2. Statistical analysis

A statistical analysis plan (PAS) will be written before the database freeze.

All statistical analyses will be performed on an intent-to-treat basis (ITT), on PP population for efficacy and on Safety population for safety.
Descriptive analyzes will be made by treatment arm.

The description data for each arm will be using median and range for continuous parameters, frequency and percentage for categorical variables.
Baseline characteristics of included patients in each arm will be compared by Kruskal-Wallis tests or Wilcoxon for continuous variables, or chi 2 or Fisher exact test for categorical variables.

The median follow-up will be calculated using the Reverse Kaplan-Meier method in each arm and overall with its confidence interval of 95%.
The primary endpoint PFS will be presented by the percentage of patients alive and without progression at 6 months with the 95% confidence interval.
All event -free survival (Progression free survival PFS, Overall Survival OS) will be estimated using the Kaplan-Meier method, and then described using medians and the rate at 6 months and 1 year with their associated 95% confidence interval.

Descriptive statistics are planned for the secondary endpoints.

Analyses of tolerance will be deferred for the safety population by treatment arm.

Incidence rates of adverse events and serious adverse events will be carried using frequencies and percentages:
Number and percentage of patients with at least one adverse event,
Number and percentage of patients with at least one adverse event of grade 3-4,
Number and percentage of patients with at least one SAE,
Number and percentage of patients with at least one adverse event and an adverse event of grade 3-4 treatment,
Number and percentage of patients with at least one adverse event resulting in discontinuation of treatment.

The number of cycles and the dose and the dose-intensities will be described as the percentage of patients with dose modification or delay with the reasons.

All statistical analyses will be performed with the Stata v10 software.

12.3. Stopping rules and early trial termination based on toxic deaths

No stopping rules will be planned.

The rate of toxic deaths in the experimental arm will be carefully monitored (According to the PV survey, the IDMC should be convocated to review cases).

12.4. Study population

Populations for analysis are defined as follow:

- Intention to treat (ITT) population for the primary endpoint = all randomized patients analyzed in their randomization arm.

- Intention to treat (ITT) population for specific secondary endpoints (objective response rate, Impact of early tumour shrinkage (>20% decrease on the 8-weekly radiological assessments) on long-term outcome (PFS and OS), predictive impact of hypomagnesemia and smoking status on treatment efficacy and outcome, safety (NCI CTCAE v 4.0 classification), quality of life (QoL, QLQ-C30 and QLQ-CR29) and translational research : all patients included in the trial (whether randomized or not)

- Per-Protocol population (PP) = eligible patients (patients presenting a major deviation from the inclusion/exclusion criteria will not be selected) and evaluable (randomized treated patients with at least one evaluation).

- Population used for the evaluation of the toxicity = all patients treated and who have received at least one dose of treatment.

12.5. Major deviations within Inclusion and Exclusion criteria:

- Histologically confirmed colorectal cancer
- KRAS and NRAS wild-type gene after analysis of mutation status from the primary tumour or metastasis

- No prior chemotherapy except for fluoropyrimidines +/- oxaliplatin-based adjuvant treatment earlier than 6 months ago
- Patient presenting with at least one measurable tumour target (≥ 10 mm) according to RECIST criteria, which has never been irradiated
- Performance Status ≤ 2 (WHO)
- Prior treatment with anti-EGFr antibodies (e.g. cetuximab / Erbitux®) or treatment with small EGFr inhibitor molecules (e.g., erlotinib / Tarceva®)

12.6. Modifications of the statistical analysis plan and initial strategy

Any modification to the initial statistical analysis plan (PAS) will be detailed with all the necessary arguments reported in an updated version of PAS. These modifications can include supplementary or exploratory analyses that were not initially planned.

13. QUALITY CONTROL AND QUALITY ASSURANCE

13.1. Monitoring committee

13.1.1. Comité de surveillance

- Will be monitored by the pharmacovigilance

13.1.2. Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will be set up to guarantee effective protection of patients, insure the ethical conduct of the trial, evaluate the benefit/risk ratio, and supervise the review of the scientific results during and at the end of the trial.

The committee may recommend the early termination of the trial if one of the following conditions is fulfilled:

- All available data from the trial or any other source of information are sufficiently convincing to influence the therapeutical practices of the majority of clinicians.

The committee has only a consultative role; it will inform the Sponsor who will decide whether the IDMC recommendation will be followed.

13.2. Quality assurance

13.2.1. 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 following data will be collected:
- Clinical examination, weight, height, vital signs
- Blood and biological test
- Adverse events and serious adverse events occurring at each cycle

During the trial, data correction request (DCFs) may be sent by the dataCenter of UNICANCER R&D located to the Biostatistical Unit of ICM, Montpellier) for data consistency validation. These forms must completed by the authorized persons the same way as the CRFs.

13.2.2. 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) 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.
- auditing the participating centers when deemed necessary,

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.

13.2.3. Auditing

Within the framework of the auditing program, the sponsor may have to conduct the audit of some participating centers. Participating centers and clinical investigators accept to comply with the audit that the sponsor or any mandated sponsor representative may conduct during a period of 10 years following the end of the study.

Participating centers and clinical investigators commit to dedicating the time necessary to the conduct of the audit and inspection procedures, to providing additional information requested by the sponsor, the competent health authority and/or any other official authority.

14. ETHICAL AND REGULATORY ISSUES

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 (annexe 2),
- the Good Clinical Practices of November 24th, 2006, defined by the International Conference on Harmonization (ICH–E6, 17/07/96),
- 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° 2011-814 of July 8th, 2011.

14.1. Authorization for the clinical trial

Before starting biomedical research on human subjects, the sponsor has the obligation to submit the trial project to the opinion of one of the committees for the protection of patients which is competent in the area where the principal investigator is practicing.

A request for authorization concerning the biomedical research project is addressed to the competent authority (ANSM) by the sponsor.

The request for substantial modifications of the initial project are submitted for authorization to the ANSM and to the relevant ethics committee for opinion by the sponsor.

The clinical trial can begin as soon as a favorable opinion has been received by the CPP and the ANSM has authorized the trial.

14.2. 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.

14.3. 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) on the initial project and the substantial amendments,
- to file the demand of authorization for the initial project and all substantial amendments with the competent authority,
- 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,
- to declare the beginning and end of the trial to the competent authority,
- to edit the final report on the trial,
- to communicate the information on the trial's results to the competent authority, the CPP 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.

14.4. 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 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 and the competent authority.

It is the responsibility of the main investigator:

- to respect the confidentiality of the trial,
- 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.

It is the responsibility of each investigator:

- 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 date, correct and sign the corrections made in the observation handbook for each patient included in 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.

14.5. Collection of human biological sample(s)

Biological studies are necessary to advance the knowledge of diseases and could help in devising newer and more effective treatments. These studies are realized using human biological samples (blood, tumor tissues) that can be collected from patients either while they receive medical cares (examination, surgery) or specifically for the research purpose.

The revision of the law of bioethics in 2004 provides a legal framework for the use and storage of human biological samples, notably regarding the patient information and solicitation of his/her consent or the right of refusal according to the modalities by which the sample is collected. The law also foresees that after the biological studies has been completed and in the case the patient does not oppose it, the samples that were not completely used may be used in subsequent scientific research.

Additionally, it must be noted that the results of biological studies may be published under the condition that all the data relative to the patients are made anonymous.

As for research aimed at studying the genetic characteristics of the patients, a consent form must be signed by each participating patient after he has been informed on the research undertaken, irrespective of the type of sample collected (already existing or specifically collected).

14.6. Sample use and storage

During the medical cares of surgical interventions, that have been (or are going to be) realized, biological, tissues and/or cells samples (blood, tumor tissues) have been (or will be) collected for medical purposes. A part of these samples will be kept and use in scientific research.
The patient will be informed of this research and, if he/she agrees, the biological samples for the research study will be:

- (1) prepared and stored using a specific technic (freezing, fixation in paraffin or with nitrogen) to ensure its long-term preservation in excellent conditions.
- (2) used in this research (*see appendix 7*).

The preparation, storage and use of the biolgical samples does not modify or imply any change with respect to the diagnosis, cares, and treatments that will be administered to the patient.

The results from this research may be published later on in scientific journals; all data will be made anonymous.

Once the research is completed and if the patient does oppose it, the samples that have not been completely used may be used in further research.

14.7. Federation of the Patients Committee for Clinical Cancer Research (FCPRCC)

The creation of the Federation of the Patient Committees for Clinical Cancer Research (FPCCCR) was initiated by the UNICANCER and the LNCC (National League for Treating Cancer). Its dedicated task is a

second reading of the clinical trial protocols. 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.

15. RESEARCH DATA PROCESSING AND DOCUMENT ARCHIVING

15.1. Data processing and ownership

15.1.1. At the level of the sponsor

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.

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).

15.1.2. In the investigational centers if digital medical records are used

In the case that digitized patient records are used in a participating center to process or store data related to the biomedical research, the center must:

a) verify and document that the computerized systems used to process the data is in conformity with the requirements in terms of data completeness, accuracy and reliablity with respect to the expected performances (quality validation);
b) set up and follow up the standardized procedures related to these systems;
c) ensure that these systems allow modifications of the collected data, that each modification is automatically documented, and that no data can be removed (i.e., any change or modification of the data must be traceable);
d) set up and maintain a security control that prevents any unauthorized access to the data;
e) establish and regularly update the list of persons authorized to access and modify the data;
f) carry out appropriate backups of the data;
g) ensure confidentiality, whenever it is applicable (e.g. during data input);
h) ensure that the computerized patient personal data are processed within the framework of the research study according to the law on ''digital information and freedom'' n° 78-17 of January 6, 1978 modified by the law n°2004-801 of August 6, 2004 and the texts regulating its application.

If data are transformed while being processed, it should always be possible to compare them with the original observations.

The computerized system used to identify the patients participating in the research must not be ambiguous and should allow the identification of all data collected for each patient while preserving their confidentiality in accordance with the law n° 78-17 modified.

15.2. 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.

16. 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.

17. 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) <u>The first author</u> 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) <u>Order of authors:</u> 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.
- With some exceptions, a member of the Inserm Unit 866 will be last author in trials sponsored or managed by FFCD, unless he/she is first author, to insure that the Inserm participation is represented. In that case, the author before the last author may be indicated as having "equally contributed" (if applicable).
- 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) <u>Oral communications:</u>

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.

18. BIBLIOGRAPHY

1. Sartore-Bianchi A, Di Nicolantonio F, Nichelatti M, et al. Multi-determinants analysis of molecular alterations for predicting clinical benefit to EGFR-targeted monoclonal antibodies in colorectal cancer. PLoS One. 2009 Oct 2;4(10):e7287.
2. Di Nicolantonio F, Martini M, Molinari F, et al. Wild-type BRAF is required for response to panitumumab or cetuximab in metastatic colorectal cancer. J Clin Oncol. 2008 Dec 10;26(35):5705-12.
3. De Roock W, Claes B, Bernasconi D, et al. Effects of KRAS, BRAF, NRAS, and PIK3CA mutations on the efficacy of cetuximab plus chemotherapy in chemotherapy-refractory metastatic colorectal cancer: a retrospective consortium analysis. Lancet Oncol. 2010 Aug;11(8):753-62.
4. Loupakis F, Ruzzo A, Cremolini C, et al. KRAS codon 61, 146 and BRAF mutations predict resistance to cetuximab plus irinotecan in KRAS codon 12 and 13 wild-type metastatic colorectal cancer. Br J Cancer. 2009 Aug 18;101(4):715-21.
5. Seymour MT, Brown SR, Richman S, et al. Panitumumab in Combination With Irinotecan for Chemoresistant Advanced Colorectal Cancer: Results of PICCOLO, a Large Randomised Trial With Prospective Molecular Stratification. ESMO : abstract 6007
6. Ducreux M, Malka D, Mendiboure J, Etienne PL, Texereau P, Auby D, Rougier P, Gasmi M, Castaing M, Abbas M, Michel P, Gargot D, Azzedine A, Lombard-Bohas C, Geoffroy P, Denis B, Pignon JP, Bedenne L, Bouché O; Fédération Francophone de Cancérologie Digestive (FFCD) 2000–05 Collaborative Group. Sequential versus combination chemotherapy for the treatment of advanced colorectal cancer (FFCD 2000-05): an open-label, randomised, phase 3 trial. Lancet Oncol 2011;12:1032-44.
7. Koopman M, Antonini NF, Douma J, Wals J, Honkoop AH, Erdkamp FL, de Jong RS, Rodenburg CJ, Vreugdenhil G, Loosveld OJ, van Bochove A, Sinnige HA, Creemers GJ, Tesselaar ME, Slee PH, Werter MJ, Mol L, Dalesio O, Punt CJ. Sequential versus combination chemotherapy with capecitabine, irinotecan, and oxaliplatin in advanced colorectal cancer (CAIRO): a phase III randomised controlled trial. Lancet 2007;370:135-142.
8. Seymour MT, Maughan TS, Ledermann JA, Topham C, James R, Gwyther SJ, Smith DB, Shepherd S, Maraveyas A, Ferry DR, Meade AM, Thompson L, Griffiths GO, Parmar MK, Stephens RJ. Different strategies of sequential and combination chemotherapy for patients with poor prognosis advanced colorectal cancer (MRC FOCUS): a randomized controlled trial. Lancet 2007;370:143-152.
9. Folprecht G, Seymour MT, Saltz L, Douillard JY, Hecker H, Stephens RJ, Maughan TS, Van Cutsem E, Rougier P, Mitry E, Schubert U, Kohne CH. Irinotecan/fluorouracil combination in first-line therapy of older and younger patients with metastatic colorectal cancer: combined analysis of 2,691 patients in randomized controlled trials. J Clin Oncol 2008;26:1443-1451.
10. Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, Berlin J, Baron A, Griffing S, Holmgren E, Ferrara N, Fyfe G, Rogers B, Ross R, Kabbinavar F. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004;350:2335-2342.
11. Glimelius B, Cavalli-Björkman N. Metastatic colorectal cancer: Current treatment and future options for improved survival Medical approach - present status. Scand J Gastroenterol. 2012 Mar;47(3):296-314. Epub 2012 Jan 16.
12. Maindrault-Goebel F, de Gramont A, Louvet C, André T, Carola E, Gilles V, Lotz JP, Tournigand C, Mabro M, Molitor JL, Artru P, Izrael V, Krulik M. Evaluation of oxaliplatin dose intensity in bimonthly leucovorin and 48-hour 5-fluorouracil continuous infusion regimens (FOLFOX) in pretreated metastatic colorectal cancer. Oncology Multidisciplinary Research Group (GERCOR). Ann Oncol.2000 Nov;11(11):1477-83.
13. André T, Louvet C, Maindrault-Goebel F, Couteau C, Mabro M, Lotz JP, Gilles-Amar V, Krulik M, Carola E, Izrael V, de Gramont A. CPT-11 (irinotecan) addition to bimonthly, high-dose leucovorin and bolus and continuous-infusion 5-fluorouracil (FOLFIRI) for pretreated metastatic colorectal cancer. GERCOR. Eur J Cancer. 1999 Sep;35(9):1343-7.
14. Labianca R, Floriani I, Cortesi E, Isa L, Zaniboni A, Marangolo M, Frontini L, Barni S, Beretta GD, Sobrero A. Alternating versus continuous "FOLFIRI" in advanced colorectal cancer (ACC): A randomized "GISCAD" trial. J Clin Oncol 24[18S]. 2006. Ref Type: Abstract
15. Maindrault-Goebel F, Lledo G, Chibaudel B, Mineur L, Andre T, Bennamoun M, Mabro M, Artru P, Louvet C, de Gramont A. Final results of OPTIMOX2, a large randomized phase II study of maintenance therapy or chemotherapy-free intervals (CFI) after FOLFOX in patients with metastatic colorectal cancer (MRC): A GERCOR study. J Clin Oncol 25[18S]. 2007.
16. Maughan TS, Adams RA, Smith CG, et al, on behalf of the MRC COIN Trial Investigators. Addition of cetuximab to oxaliplatin-based first-line combination chemotherapy for treatment of advanced

colorectal cancer: results of the randomised phase 3 MRC COIN trial. *Lancet* 2011; published online June 4. DOI:10.1016/S0140-6736(11)60613-2.
17. Sobrero A, Guglielmi A, Grossi F, Puglisi F, Aschele C. Mechanism of action of fluoropyrimidines: relevance to the new developments in colorectal cancer chemotherapy. Semin Oncol. 2000 Oct;27(5 Suppl 10):72-7.
18. Tournigand C, Cervantes A, Figer A, Lledo G, Flesch M, Buyse M, Mineur L, Carola E, Etienne PL, Rivera F, Chirivella I, Perez-Staub N, Louvet C, André T, Tabah-Fisch I, de Gramont A. OPTIMOX1: a randomized study of FOLFOX4 or FOLFOX7 with oxaliplatin in a stop-and-Go fashion in advanced colorectal cancer--a GERCOR study. J Clin Oncol. 2006 Jan 20;24(3):394-400.
19. Labianca R, Sobrero A, Isa L, Cortesi E, Barni S, Nicolella D, Aglietta M, Lonardi S, Corsi D, Turci D, Beretta GD, Fornarini G, Dapretto E, Floriani I, Zaniboni A; Italian Group for the Study of Gastrointestinal Cancer-GISCAD. Intermittent versus continuous chemotherapy in advanced colorectal cancer: a randomised 'GISCAD' trial. Ann Oncol. 2011 May;22(5):1236-42. Epub 2010 Nov 15.
20. Douillard JY, Cunningham D, Roth AD et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. Lancet 2000; 355: 1041–1047.
21. Chibaudel B, Maindrault-Goebel F, Lledo G et al. Can chemotherapy be discontinued in unresectable metastatic colorectal cancer? The GERCOR OPTIMOX2 study. J Clin Oncol 2009; 27: 5727–5733.
22. Hochster HS. Stop and go: yes or no? J Clin Oncol 2009; 27: 5677–5679.
23. Adams RA, Meade AM, Seymour MT, Wilson RH, Madi A, Fisher D, Kenny SL, Kay E, Hodgkinson E, Pope M, Rogers P, Wasan H, Falk S, Gollins S, Hickish T, Bessell EM, Propper D, Kennedy MJ, Kaplan R, Maughan TS; MRC COIN Trial Investigators. Intermittent versus continuous oxaliplatin and fluoropyrimidine combination chemotherapy for first-line treatment of advanced colorectal cancer: results of the randomised phase 3 MRC COIN trial. Lancet Oncol. 2011 Jul;12(7):642-53. Epub 2011 Jun 5.
24. Allen WL, Stevenson L, Coyle VM, Jithesh PV, Proutski I, Carson G, Gordon MA, Lenz HJ, Van Schaeybroeck S, Longley DB, Johnston PG. A systems biology approach identifies SART1 as a novel determinant of both 5-fluorouracil and SN38 drug resistance in colorectal cancer. Mol Cancer Ther. 2012 Jan;11(1):119-31. Epub 2011 Oct 25.
25. Ebert MP, Tänzer M, Balluff B, Burgermeister E, Kretzschmar AK, Hughes DJ, Tetzner R, Lofton-Day C, Rosenberg R, Reinacher-Schick AC, Schulmann K, Tannapfel A, Hofheinz R, Röcken C, Keller G, Langer R, Specht K, Porschen R, Stöhlmacher-Williams J, Schuster T, Ströbel P, Schmid RM. TFAP2E-DKK4 and chemoresistance in colorectal cancer. N Engl J Med. 2012 Jan 5;366(1):44-53.
26. Correale P, Rotundo MS, Botta C, Del Vecchio MT, Ginanneschi C, Licchetta A, Conca R, Apollinari S, De Luca F, Tassone P, Tagliaferri P. Tumor Infiltration by T Lymphocytes Expressing Chemokine Receptor 7 (CCR7) Is Predictive of Favorable Outcome in Patients with Advanced Colorectal Carcinoma. Clin Cancer Res. 2012 Feb 1;18(3):850-857. Epub 2011 Dec 5.
27. Real FX, Rettig WJ, Chesa PG, et al. Expression of epidermal growth factor receptor in human cultured cells and tissues: relationship to cell lineage and stage of differentiation. *Cancer Res* 1986; 46:4726-4731.
28. Cunningham D, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med* 2004; 351:337-345.
29. Badarinath SM, Mitchell EP, Jennis A, et al. Cetuximab plus FOLFOX for colorectal (EXPLORE): preliminary safety analysis of a randomized phase III trial. *Proc Am Soc Clin Oncol* 2004; 23:253 (Abstract #3531).
30. Rougier P, Raoul JL, Van Laethem JL, et al. Cetuximab + FOLFIRI as first-line treatment for metastatic colorectal cancer. *Proc Am Soc Clin Oncol* 2004; 23:248 (Abstract #3513).
31. Maughan TS, Adams RA, Smith CG, et al, on behalf of the MRC COIN Trial Investigators. Addition of cetuximab to oxaliplatin-based first-line combination chemotherapy for treatment of advanced colorectal cancer: results of the randomised phase 3 MRC COIN trial. *Lancet* 2011; published online June 4. DOI:10.1016/S0140-6736(11)60613-2.
32. Daanish Hoda, George R Simon, and Christopher R Garrett Targeting colorectal cancer with anti-epidermal growth factor receptor antibodies: focus on panitumumab Ther Clin Risk Manag. 2008 December; 4(6): 1221–1227. Published online 2008 December.
33. Colucci G, Giuliani F, Garufi C, Mattioli R, Manzione L, Russo A, Lopez M, Parrella P, Tommasi S, Copetti M, Daniele B, Pisconti S, Tuveri G, Silvestris N, Maiello E. Cetuximab plus FOLFOX-4 in untreated patients with advanced colorectal cancer: a Gruppo Oncologico dell'Italia Meridionale Multicenter phase II study. Oncology. 2010;79(5-6):415-22. Epub 2011 Apr 7.

34. Murphy JE, Ryan DP. American Society of Clinical Oncology 2010 colorectal update. Expert Rev Anticancer Ther. 2010 Sep;10(9):1371-3.
35. Blanke CD, Goldberg RM, Grothey A, Mooney M, Roach N, Saltz LB, Welch JJ, Wood WA, Meropol NJ; NCI GI Steering Committee Colon Cancer Task Force. KRAS and colorectal cancer: ethical and pragmatic issues in effecting real-time change in oncology clinical trials and practice. Oncologist. 2011;16(8):1061-8. Epub 2011 Jul 7.
36. Beata Zahorowska, Philip J. Crowe and Jia-Lin Yang Combined therapies for cancer: a review of EGFR-targeted monotherapy and combination treatment with other drugs. J Cancer Res Clin Oncol. 2009 Sep;135(9):1137-48. Epub 2009 Jun 17.
37. J. Tabernero, E. Aranda, A. Gomez, B. Massuti, J. Sastre, A. Abad, M. Valladares, F. Rivera, M. Safont, E. Diaz-Rubio Phase III study of first-line XELOX plus bevacizumab (BEV) for 6 cycles followed by XELOX plus BEV or single-agent (s/a) BEV as maintenance therapy in patients (pts) with metastatic colorectal cancer (mCRC): The MACRO Trial (Spanish Cooperative Group for the Treatment of Digestive Tumors [TTD]). J Clin Oncol 28[15s]. 2010
38. Etude Prodige 9 phase III Version 1.0 du 21 06 2011 Page 31 sur 80
39. Harpreet Wasan, Richard Adams, Richard Wilson, Cheryl Pugh, David Fisher, Ayman Madi, Bruce Sizer, Rachel Butler, Angela Meade, Tim Maughan on behalf of the MRC COIN-B Trial Investigators Results of the two-arm phase II randomised MRC COIN-B (CR 11) trial ESMO conference 2011

19. APPENDICES

- Appendix 1 : Evaluation of the patient's performance status ECOG or WHO
- Appendix 2 : Declaration of Helsinki
- Appendix 3 : RECIST V1.1
- Appendix 4 : NCI-CTCAE Version 4.0
- Appendix 5 : Clinical Investigator's brochure
- Appendix 6 : Translational research
- Appendix 7 : QLQ C30
- Appendix 8 : QLQ CR29
- Appendix 9 : Score de Köhne

Appendix 1 :
Performance status evaluation – WHO scale

Performance status ECOG-ZUBROD/ WHO	value
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 2 :
World Medical Association
Declaration of Helsinki

WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington, DC, USA, October 2002
(Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo, Japan, October 2004
(Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, Korea, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects**,** including research on identifiable human material and data.
The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.
2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.
3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."
5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.
6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.
7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
8. In medical practice and in medical research, most interventions involve risks and burdens.
9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.
10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.
12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.
14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.
15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.
16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.
17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.
18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.
19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.
20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.
21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.
22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.
23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.
24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.
25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.
26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.

27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.
28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.
29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.
30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE
31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:

- The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
- Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.
34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.
35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

Appendix 3 – Classification RECIST V1.1

quick reference (Eur. J. Cancer, 45(2009), 228-247 [47])

Full article available on : http://ctep.cancer.gov/

"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

French summary :

Lésions à l'inclusion:

Les lésions et les ganglions sont classés individuellement comme étant mesurable ou non mesurable.

Maladie mesurable

Pour qu'une lésion soit jugée mesurable, au moins une de ses dimensions doit pouvoir être mesurée de façon précise (la dimension la plus longue, dans le plan de la prise de mesures, devra être rapportée).
Pour être mesurables, les lésions doivent présenter une mesure minimum de

- ≥ 10 mm au scanner (pour autant que la largeur de bande du CT-scan soit d'au maximum 5 mm)
- ≥ 10 mm par examen clinique (mesurable par pied à coulisse) (les lésions qui ne peuvent être mesurées précisément doivent être répertoriées comme étant non-mesurables)
- 20 mm par radiographie (=X-ray) du thorax
- Pour qu'un ganglion lymphatique malin soit considéré pathologique et mesurable, celui-ci doit présenter un plus petit axe ≥ 15 mm (le plus petit axe étant l'axe perpendiculaire à la plus grande dimension du ganglion). Seule la longueur de ce plus petit axe sera rapportée tant à l'entrée que durant le suivi.

Maladie non-mesurable

Toutes les autres lésions, incluant les petites lésions (plus grand diamètre < 10 mm au scanner ou les ganglions lymphatiques dont le plus petit axe est ≥ 10 mm et < 15 mm) ainsi que les lésions réellement non-mesurables : maladie leptoméningée, ascite, pleurésie, péricardite, maladie inflammatoire du sein, lymphangites carcinomateuses pulmonaires ou cutanées, les masses abdomino-pelviennes décelées par l'examen clinique mais non confirmées à l'imagerie et les lésions kystiques.
Nota bene : les lésions osseuses, les lésions kystiques simples et les lésions ayant précédemment reçu un traitement local nécessitent une considération particulière (cf commentaires ci-dessous).

Lésions cibles

Les lésions cibles sont sélectionnées parmi les lésions mesurables que présente le malade à l'entrée de l'étude. **Au maximum 5 lésions cibles sont sélectionnées au total avec un maximum de 2 lésions cibles par organe**. La sélection des lésions cibles s'opérera de façon à être représentative de tous les organes envahis, en choisissant les lésions les plus grandes (dans leur plus grande dimension) qui de plus, pourront être suivies tout au long de l'essai avec la méthode utilisée lors de l'examen initial. Les ganglions lymphatiques peuvent être considérés comme lésions cibles si leur plus petit axe (mesuré au scanner) est ≥ 15 mm.

C'est la somme des diamètres de ces lésions cibles (plus grand axe pour les lésions, et plus petit axe pour les ganglions) qui sera suivie au long de l'essai pour évaluer la réponse ou la progression.

Lésions non-cibles

Toutes les autres lésions sont identifiées comme lésions non-cibles et sont également relevées à l'inclusion. Elles ne sont pas mesurées mais sont suivies tout au long de l'essai.

Critères de réponse au traitement :

Lésions cibles :

Réponse complète (RC) : Disparition de toutes les lésions. De plus, tous les ganglions lymphatiques (cible ou non-cible), doivent avoir atteint une dimension < 10 mm dans leur *plus petit* axe.

Attention : les ganglions sélectionnés comme lésions cibles doivent toujours être mesurés (dimension du plus petit axe dans le plan anatomique utilisé pour l'examen BASELINE), même s'ils diminuent en taille durant l'étude et que leur petit axe devient < 10 mm. Dès lors, lorsque des ganglions sont utilisés comme lésion cible, la « somme » des dimensions des lésions n'est pas nécessairement nulle, même en cas de réponse complète, puisqu'un ganglion normal est défini comme ayant un plus petit axe < 10 mm. Pour obtenir une réponse complète chaque ganglion doit avoir atteint une dimension < 10 mm dans son plus petit axe.

Réponse partielle (RP) : Diminution d'au moins 30 % de la somme des diamètres des lésions cibles par rapport à la somme initiale des diamètres (Examen BASELINE).

Progression (PD) : Augmentation ≥ 20 % de la somme des diamètres des lésions cibles par rapport à la plus petite somme des diamètres observée durant l'étude (NADIR), y compris la visite de baseline. En plus de cette augmentation relative de 20%, cette somme doit augmenter d'au moins 0,5 cm.
Nota bene : l'apparition d'une ou plusieurs nouvelles lésions est également considérée comme progression.
Attention : s'il existe une progression par rapport au NADIR et une réponse par rapport à l'examen BASELINE, c'est la progression qui prévaut.

Stabilisation (SD) : Ni RP (ou RC), ni PD.

Lésions non-cibles

Réponse complète : Disparition de toutes les lésions non-cibles et normalisation des marqueurs tumoraux. Tous les ganglions lymphatiques doivent avoir atteint un petit diamètre < 10 mm.
Réponse incomplète - Stabilisation : Persistance d'au moins une lésion non-cible et/ou marqueur tumoral au-dessus des normales.
Progression : Augmentation **indiscutable** de la taille des lésions non-cibles ou apparition d'une nouvelle lésion.

Réponse globale :

Lésions cibles	Lésions non-cibles	Nouvelle lésion		Réponse globale
RC	RC	Non	=	**RC**
RC	Non RC/Non PD	Non	=	**RP**
RC	Non évalué	Non	=	**RP**
RP	Non PD ou pas tous évalués	Non	=	**RP**
SD	Non PD ou pas tous évalués	Non	=	**SD**
Pas tous évalués	Non PD	Non	=	**Non-évaluable**
PD	Indifférent	Oui ou non	=	**PD**
Indifférent	PD	Oui ou non	=	**PD**
Indifférent	Indifférent	Oui	=	**PD**

Commentaires relatifs à la mesurabilité des lésions à l'entrée

Lésions osseuses :

- l'imagerie par scintigraphie osseuse, PET-scan et « plain films » ne sont pas considérées comme étant adéquates pour la mesure des lésions osseuses. Cependant, ces techniques peuvent être utilisées pour confirmer la présence ou la disparition de lésions osseuses
- Les lésions osseuses de type lytique ou de type mélangé lytique-ostéoblastique, qui contiennent une composante identifiable de tissus mous, peuvent être considérés comme des lésions mesurables, pour autant qu'elles puissent être mesurées par des techniques d'imagerie cross-sectionnelle de type CT ou IRM, et que la composante de tissus mous remplissent les conditions de mesurabilité indiquées plus haut.

Lésions kystiques :

- Les lésions qui correspondent au diagnostic de simple kyste par radiographie ne sont pas considérées comme des lésions malignes (ni mesurables, ni non-mesurables)
- Les lésions kystiques de type malin peuvent être prises en compte comme lésion mesurable pour autant qu'elles remplissent les critères de mesurabilité définis plus haut. Cependant, si le patient présente d'autres lésions non kystiques, celles-ci seront préférablement choisies comme lésion cible.

Lésions préalablement traitées localement :

- Les lésions situées dans une région préalablement irradiée ou ayant reçu une autre thérapie loco-régionale ne sont en général pas considérées comme étant mesurables, à l'exception des lésions ayant progressé depuis le traitement local. Le protocole de l'étude doit détailler les conditions spécifiques permettant de considérer de telles lésions comme étant mesurables.

Appendix 4– Toxicity Criteria (CTCAE)

Please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) (Publish Date May 28, 2009)**, separately joined to this protocol or available on :**

NATIONAL CANCER INSTITUTE

Cancer Therapy Evaluation Program

http://ctep.cancer.gov/

Appendix 5 – summary of product characteristics

See Investigator and Pharmacist workbook

Appendix 6:
Translational research (Blood and tissues)

À l'inclusion (avant la première administration de l'association FOLFIRI + Cetuximab) chaque centre offrira au patient la possibilité de participer à l'étude biologique. Si le patient accepte, le type de prélèvement réalisé sera consigné au même moment que la demande de randomisation.

SANG

Une quantification des cellules tumorales circulantes (CTC) et de l'ADN tumoral libre dans les échantillons sanguins sera effectuée 4 fois pendant l'évaluation

1/ Visite initiale : avant l'instauration de la chimiothérapie par l'association FOLFIRI plus cetuximab chez tous les patients
2/ Après 4 mois de l'association FOLFIRI plus cetuximab chez tous les patients (lors de la randomisation, juste avant la période de traitement d'entretien ou d'observation, y compris chez les patients non éligibles pour la randomisation)
3/ 1 mois après la randomisation dans chaque groupe (après un mois de traitement d'entretien ou d'observation)
4/ Lors de la première progression (sous traitement d'entretien ou d'observation) dans chaque groupe

Si le prélèvement d'un échantillon sanguin est prévu, immédiatement après l'inclusion du patient, le centre recevra une boîte de transport pour matériaux biologiques à utiliser pour envoyer les 2 échantillons de sang aux deux laboratoires de recherche translationnelle mentionnés ci-dessous.

Les échantillons de sang seront recueillis par ponction de sang veineux réalisée au cours de soins médicaux ou d'un examen nécessaire pour le patient. En aucun cas il ne sera possible de prélever des échantillons supplémentaires pour la recherche translationnelle.

Pour la quantification des CTC, les échantillons de sang (7,5 ml par test) seront recueillis dans des tubes collecteurs CellSave™ (Immunicon Inc, Huntingdon Valley, Pennsylvanie) et envoyés à température ambiante au centre de collecte (Françoise Farace, Laboratoire de recherche translationnelle, INSERM U981, Gustave Roussy 114 rue Édouard Vaillant 94805 Villejuif)

Pour la quantification de l'ADN, 10 ml de sang seront recueillis (tube EDTA de 10ml). Après centrifugation**, le plasma** ainsi que le « buffy coat » contenant les leucocytes et plaquettes, seront extraits et congelé à -80°C avant d'être envoyés au centre de collecte (Unité ISERM U775, Centre Universitaire des Saints-Pères, 45 rue des Saints-Pères, 75006 PARIS). L'envoi des échantillons congelés se fera 2 fois par an.

TISSUS (recherche optionnelle)

Biomarqueurs tumoraux (consentement spécifique)

Des biopsies séquentielles fixées et congelées consistant en une biopsie de la tumeur et du tissu normal **avant tout traitement** et une biopsie tumorale lors de la progression **sous FOLFIRI-cetuximab (y compris les malades non randomisés pour progression d'emblée sous FOLFIRI-cetuximab)** seront réalisées en vue d'une analyse de biomarqueurs, notamment :

- expression intratumorale des phosphoprotéines de signalisation en aval de l'EGFR et des voies PI3K/AKT,
- Analyse par biopuce génomique sur des échantillons de tissu congelés afin d'identifier une signature d'expression génique prédictive de la réponse et/ou de la résistance à l'association FOLFIRI plus cetuximab. L'objectif de cette analyse est d'identifier l'activation des voies moléculaires impliquées dans la réponse de la tumeur et dans la résistance acquise au cetuximab et à FOLFIRI décelée dans les échantillons tumoraux avant ou pendant le traitement

La biopsie ou la ponction sera réalisée selon les recommandations locales. Lors de la réalisation de la biopsie deux échantillons seront collectés, un échantillon sera congelé en azote liquide, sans délai, sur le lieu de réalisation de la biopsie et conservé dans les mêmes conditions. Le second échantillon sera collecté dans un fixateur formolé avec une durée de fixation de 30 minutes (maximum 1 heure). Les échantillons fixés seront conservés à 4°C après inclusion dans la paraffine. Les procédures de recueil pourront être modifiées en fonction de l'expertise acquise au cours du temps et permettant une amélioration de la qualité des analyses. Si un acte chirurgical est programmé, ces échantillons pourront être également prélevés à ce moment là.

Dans le même temps, une biopsie du tissu normal avant traitement (de l'organe à l'origine du cancer) sera également réalisée en suivant la même procédure que ci-dessus.

Une biopsie supplementaire sera effectuée lors **de la progression de la maladie sous FOLFIRI-cetuximab** dans le but d'analyser les transformations biologiques qui surviennent au cours du temps et qui sont à l'origine d'une résistance au traitement de l'étude.

Les échantillons tissulaires seront conservés dans chaque centre participant et collectés après la fin de l'étude

RECAPITULATIF DES PRELEVEMENTS A REALISER

Période	**Avant l'inclusion#**	**A l'inclusion Avant tout traitement**			**Lors de la randomisation****		**1 mois après la randomisation**		**Lors de la 1ère progression sous traitement de maintenance ou pause complète**		**Lors de la 2ème progression sous FOLFIRI-cetuximab*****
Matériau	Tissu	Tissu*	Sang		Sang		Sang		Sang		Tissu*
Quantité	Bloc diagnostique	biopsie de tissu tumoral et de tissu normal	7,5 ml dans tube Cell Save	10 ml dans tube EDTA + centrifugation	7,5 ml dans tube Cell Save	10 ml dans tube EDTA + centrifugation	7,5 ml dans tube Cell Save	10 ml dans tube EDTA+ centrifugation	7,5 ml dans tube Cell Save	10 ml dans tube EDTA+ centrifugation	biopsie de tissu tumoral
Condition de stockage et de Transport	T°ambiante	4°C et -80°C Tous les 6 mois environ	Immédiatement	-80°C, tous les 6 mois environ	Immédiate-ment	-80°C, tous les 6 mois environ	Immédiate-ment	-80°C, tous les 6 mois environ	Immédiatement	-80°C, tous les 6 mois environ	4°C et -80° Tous les 6 mois environ
Transfert	Immédiatement	4°C et Congelé	Tempéra-ture ambiante	Congelé	Températu-re ambiante	Congelé	Température ambiante	Congelé	Température ambiante	Congelé	4°C et Congelé
Lieu de stockage	détermination centralisée des statuts KRAS et NRAS à l'ISERM U775 des St Pères	CRB de Lyon	Gustave Roussy	ISERM U775 St Pères	Gustave Roussy	ISERM U775 St Pères	Gustave Roussy	ISERM U775 St Pères	Gustave Roussy	ISERM U775 St Pères	CRB du Centre Léon Bérard

Vérifier la présence des gènes KRAS et NRAS sauvages. Pour cela, une relecture centralisée des blocs diagnostics sera effectuée avant l'inclusion des patients dans l'étude.

*recherche optionnelle, **idem pour les patients non éligibles pour la randomisation, ***idem pour patients non randomisés pour progression d'emblée sous FOLFIRI-cetuximab

APPENDIX 7 :
QLQ C30 and CR29

ENGLISH

EORTC QLQ – CR29

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
31. Did you urinate frequently during the day?	1	2	3	4
32. Did you urinate frequently during the night?	1	2	3	4
33. Have you had any unintentional release (leakage) of urine?	1	2	3	4
34. Did you have pain when you urinated?	1	2	3	4
35. Did you have abdominal pain?	1	2	3	4
36. Did you have pain in your buttocks/anal area/rectum?	1	2	3	4
37. Did you have a bloated feeling in your abdomen?	1	2	3	4
38. Have you had blood in your stools?	1	2	3	4
39. Have you had mucus in your stools?	1	2	3	4
40. Did you have a dry mouth?	1	2	3	4
41. Have you lost hair as a result of your treatment?	1	2	3	4
42. Have you had problems with your sense of taste?	1	2	3	4

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
43. Were you worried about your health in the future?	1	2	3	4
44. Have you worried about your weight?	1	2	3	4
45. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
46. Have you been feeling less feminine/masculine as a result of your disease or treatment?	1	2	3	4
47. Have you been dissatisfied with your body?	1	2	3	4
48. Do you have a stoma bag (colostomy/ileostomy)? (please circle the correct answer)	Yes		No	

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
Answer these questions ONLY IF YOU HAVE A STOMA BAG, if not please continue below:				
49. Have you had unintentional release of gas/flatulence from your stoma bag?	1	2	3	4
50. Have you had leakage of stools from your stoma bag?	1	2	3	4
51. Have you had sore skin around your stoma?	1	2	3	4
52. Did frequent bag changes occur during the day?	1	2	3	4
53. Did frequent bag changes occur during the night?	1	2	3	4
54. Did you feel embarrassed because of your stoma?	1	2	3	4
55. Did you have problems caring for your stoma?	1	2	3	4

Answer these questions ONLY IF YOU DO NOT HAVE A STOMA BAG:				
49. Have you had unintentional release of gas/flatulence from your back passage?	1	2	3	4
50. Have you had leakage of stools from your back passage?	1	2	3	4
51. Have you had sore skin around your anal area?	1	2	3	4
52. Did frequent bowel movements occur during the day?	1	2	3	4
53. Did frequent bowel movements occur during the night?	1	2	3	4
54. Did you feel embarrassed because of your bowel movement?	1	2	3	4

During the past 4 weeks:	Not at All	A Little	Quite a Bit	Very Much
For men only:				
56. To what extent were you interested in sex?	1	2	3	4
57. Did you have difficulty getting or maintaining an erection?	1	2	3	4

For women only:				
58. To what extent were you interested in sex?	1	2	3	4
59. Did you have pain or discomfort during intercourse?	1	2	3	4

APPENDIX 8 :
QLQ C30

ENGLISH

EORTC QLQ-C30 (version 3)

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.

Please fill in your initials: |___|___|

Your birthdate (Day, Month, Year): |___|___|___|___|___|___|___|___|

Today's date (Day, Month, Year): 31 |___|___|___|___|

		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 : Score de Köhne

(Facteurs pronostiques de survie en cas de maladie métastatique traitée par 5FU)

Score (Risque)	**Définition**
1 (Faible)	OMS 0-1, 1 site envahi
2 (Intermédiaire)	OMS 0-1, plus d'1 site envahi et phosphatases alcalines < 300 UI/L **ou** OMS > 1, Globules blancs < 10.10^9/L (10 000 /μL), 1 seul site envahi
3 (Haut)	OMS 0-1, plus d'1 site envahi, et phosphatases alcalines > 300 UI/L **ou** OMS > 1, plus d'1 site envahi **ou** Globules blanc ≥ 10.10^9/L (10 000 /μL)