Safety, tolerability and efficacy of regorafenib in combination with FOLFIRINOX in patients with RAS-mutated metastatic colorectal cancer: a dose-escalation, phase I/II trial

FOLFIRINOX-R

N°Study Sponsor	N°EudraCT
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CONFIDENTIAL

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ABBREVIATIONS

List of abbreviations	Explanation
AE	Adverse Event
ALP	AlkaLine Phosphatase – phosphatase alcaline
ALT	Alanine aminotransferase/glutamic pyruvic Transaminase/sGPT
ANSM	Agence nationale de sécurité du médicament et des produits de santé (French National Agency of Medicines and Health Products Safety)
Anti-HER1	Anticorps dirigé contre le récepteur Erb2 du facteur de croissance épidermique humain
AST	Aspartate aminotransferase/glutamic oxaloacetic Transaminase/sGOT
AUC	Area under curve – aire sous la courbe
β-HCG	Beta Human Chorionic Gonadotropin
BICR	Blinded independent central review
BSA	Body Surface Area
CA 19-9	Carbohydrate Antigen 19-9
CBC	Complete Blood Count
CCRm	Cancer colorectal métastatique
CEA	Carcino-Embryogenic Antigen
cfDNA	Circulating cell-Free Desoxy-Ribonucleic Acid Complete Blood Count
CKD-EPI	Chronic Kindney Disease – Epidemiology Collaboration
CPP	Comité de protection des personnes (Ethic Comittee)
CRA	Clinical Research Associate
CR	Complete response
2-CT	Bichimiothérapie
3-CT	Trichimiothérapie
CT Scan	Computed Tomography Scanner
DCF	Data Clarification Form
DCR	Disease control rate – Taux de contrôle de la maladie
DDR1	Discoidin Domain Receptor tyrosine kinase 1
DLT	Dose Limiting Toxicity – Toxicité limitant la dose
DPD	DihydroPyrimidine Dehydrogenase
DPR	DeePness of Response – profondeur de la réponse
DMT	Dose maximale tolérée
ECG	ElectroCardioGram - électrocardiogramme
ECOG	Eastern Cooperative Oncology Group
e-CRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
EI	Evénement indésirable
EORTC	European Organisation for Research and Treatment of Cancer

EUDRACT	European Union Drug Regulating Authorities Clinical Trials
5-FU	5 FluoroUracil
G-CSF	Granulocyte Colony-Stimulating Factor
GGT	Gamma-Glutamyl Transferase
Hb	Hemoglobin
HR	Hazard Ratio
ICM	Montpellier Cancer Institute
INCA	Institut National du CAncer
INR	International Normalized Ratio
ISC	Independent Scientific Committee
ITT	Intention-To-Treat
LDH	Lactate Dehydrogenase
LLN	Lower Limit Normal
LIN	Limite inférieure à la normale
LSN	Limite supérieure à la normale
mCRC	Metastatic Colorectal Cancer
MDRD	Modification of Diet in Renal Disease
MRI	Magnetic Resonance Imaging
MS	Maladie stable
MTD	Maximum Tolerated Dose
NCI/ CTCAE	National Cancer Institute (US) Common terminology criteria for adverse events
NYHA	New-York Heart Association
ORR	Objective response nude
OS	Overall survivall
PFS	Progression Free Survival
PR	Partial Response
PT	Prothrombine time – temps de prothrombine
PTT	Partial Thromboplastin Time – temps de prothrombine partielle
R	Taux de résection
RAS	RAt Sarcoma viral oncogene homolog
RBC	Red Blood Count
RC	Réponse complète
RECIST	Response Evaluation Criteria in Solid Tumors
RP	Réponse partielle
RP2D	Recommended Phase II Dose – dose recommandée pour la phase II
SAE	Serious Adverse Event
SD	Stable Disease
SG	Survie globale
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TSH	Thyroid stimulating hormone

UGT1A1	Uridine diphosphate Glucuronosyl Transferase 1A1
ULN	Upper Limit Normal
WBC	White Blood Count

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SYNOPSIS (English)	
TITLE	**Safety, tolerability and efficacy of regorafenib in combination with FOLFIRINOX in patients with *RAS*-mutated metastatic colorectal cancer: a dose-escalation, phase I/II trial**
SYNOPSIS VERSION	1
PATHOLOGY	Metastatic colorectal cancer
PROTOCOL CODES	**Acronym**: FOLFIRINOX-R **Sponsor Code**: PROICM 2018-08 FOL **EUDRACT**: 2018-003541-42
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STUDY DESIGN	Prospective, multicenter, open-label, uncontrolled phase I/II trial
NUMBER OF PLANNING PATIENT	87 patients out of about 174 screened patients

BACKGROUND AND RATIONALE	**Colorectal cancer** (CRC) is a major cause of morbidity and mortality globally. More than 50% of patients can be expected to develop metastatic disease, and most of these patients will require palliative systemic therapy. The primary goal for patients who present with technically resectable liver metastases is definitely cure, with R0 resection as the primary goal. Consequently, any patient with limited liver and/or lung metastases should be considered a candidate for potential secondary resection as there are no criteria that allow physicians to distinguish between those patients for whom purely palliative treatment and those or whom potentially curative treatment is appropriate. Although survival times are slightly shorter for patients who undergo conversion therapy followed by surgery than for patients with initially resectable metastatic disease, they are far better than if resection is not carried out at all (1). As per ESMO guidelines, first-line therapy commonly involves the doublet (2-CT) regimens of 5-fluorouracil, folinic acid, and either oxaliplatin (FOLFOX) or irinotecan (FOLFIRI). The addition of targeted therapies, such as bevacizumab (a pure anti-angiogenic agent which binds circulating VEGF-A), cetuximab, and panitumumab, to FOLFOX or FOLFIRI may be helpful to some patients in improving tumor response and ultimately overall survival. The cytotoxic triplet (3-CT) FOLFOXIRI with or without bevacizumab may be an option in selected fit and motivated patients when cytoreduction (tumour shrinkage) is needed to undergo conversion therapy (1). **RAS mutations** are found in about 50% of mCRC tumors. As recently rephrased by Modest et al. (2) these mutations exclude affected patients from epidermal growth factor receptor (EGFR)-directed therapy. Besides their negative predictive value, RAS mutations may also carry distinct prognostic information. Modest et al. (2) studied the prognosis by RAS status of a total of 1239 mCRC patients from five randomized trials studying 2-CT. Actually, PFS and OS were significantly influenced by molecular subgroups. Multivariate comparison of PFS and OS in patients with mutant tumors versus patients with non-mutated tumors revealed a negative prognostic effect of RAS mutations. Interestingly, the negative prognostic role of these mutations was consistently observed across different treatment regimens (subgroups of irinotecan- and oxaliplatin-treated patients as well as in bevacizumab- and non-bevacizumab-treated patients). Median PFS and OS were 10.3 vs. 9.5 months and 26.9 vs. 21.1 months in RAS-wildtype (and BRAF-wildtype) and RAS-mut patients, respectively 2).The TRIBE consortium reported that a 3-CT (FOLFOXIRI) combined with bevacizumab provided a significantly longer PFS (the primary end-point of the study) than did the 2-CT FOLFIRI plus bevacizumab (3, 4). In the subgroup of RAS- and BRAF-wild-type patients, those in the FOLFOXIRI plus bevacizumab group reported a median PFS of 13.7 months (95% CI, 10.1-18.1) compared with 12.2 months (95%CI, 9.5-14.4) in the FOLFIRI plus bevacizumab group (HR 0.85, 95%CI 0.55-1.3) (4).

	Later on, the same group reported that FOLFOXIRI plus bevacizumab provided a significantly longer overall survival than the FOLFIRI plus bevacizumab group (HR 0.80, 95%CI 0·65–0·98; p=0·03) (4). Looking at survival by RAS status, Cremolini et al. (4) reported that median OS was 37.1 months (95%CI, 29.7–42.7) in the RAS- and BRAF-wild-type subgroup compared with 25.6 months (95%CI, 22.4–28.6) in the RAS-mut subgroup (HR 1.49, 95%CI, 1.11–1·99). Interestingly, median PFS was 13.7 months (95% CI 10.1–18.1) in the RAS-wild-type subgroup treated with FOLFOXIRI plus bevacizumab, while PFS data were not given for the RAS-mut patients (4). However, for these RAS-mut patients, it was possible to estimate the median PFS (i.e. 9.4 months) from the Kaplan-Meier curve which was provided (4). **Regorafenib** is a small-molecule inhibitor of multiple membrane-bound and intracellular kinases RET, VEGFR 1, 2, 3, c-Kit, PDGFR-α, β, FGFR1, 2, TIE2, DDR1, DDR2, Trk2A, Eph2A, RAF-1, BRAF, BRAFV600E, SAPK2, PTK5, and Abl. Beyond its well-known antiangiogenic properties, regorafenib has also less-known anti-proliferative activities in human colon cancer cell lines. Interestingly, regorafenib potently inhibits growth of patient-derived CRC xenografts alone and in combination with irinotecan (5-7). Regorafenib is approved for refractory mCRC patients (8), for locally advanced, unresectable or metastatic GIST patients and for HCC patients previously treated with sorafenib. The recommended dose is 160 mg (40 mg × 4 tablets) orally, once daily for the first 21 days of each 28-day cycle. Two phase III trials demonstrated a significant overall survival benefit for regorafenib over placebo in patients with mCRC who progressed on standard therapies (8, 9). Two phase II trials studied the safety and efficacy profile of regorafenib when combined to chemotherapy in patients with mCRC (10, 11). In vitro data indicate that both regorafenib and its metabolite M-2 inhibit glucuronidation mediated by UGT1A1 and UGT1A9 (whereas M-5 only inhibits UGT1A1), hence triggering potential pharmacokinetic interactions. The study from Schultheis et al. (10) was designed to explore whether addition of regorafenib to FOLFOX or FOLFIRI could be feasible as a treatment of mCRC, in terms of safety and pharmacokinetic interactions of the various drug components of the regimen. Forty-five patients were treated every 2 weeks with 5-fluorouracil 400 mg/m² bolus then 2400 mg/m² over 46 h, folinic acid 400 mg/m², and either oxaliplatin 85 mg/m² or irinotecan 180 mg/m². On days 4–10, patients received regorafenib 160 mg orally once daily. Drug-related adverse events resulted in dose modification, dose interruption, or permanent discontinuation of study treatment in 31 (69%) patients overall (18 [72%] FOLFOX and 13 [65%] FOLFIRI). Dose reduction or dose interruption of at least one of the chemotherapy components was observed in 52% of patients treated with FOLFOX and 65% of patients receiving FOLFIRI. A dose reduction of 5-fluorouracil due to AEs was necessary in 18% of administered cycles. 5-Fluorouracil administration was omitted

	in 8% of cycles. Oxaliplatin and irinotecan doses were reduced in 11% and 12% and interrupted in 11% and 5% of administered cycles, respectively. Actually, regorafenib had acceptable tolerability in combination with chemotherapy. The most frequent grade 3-4 AEs were: neutropenia (45%), Hand-Foot Skin Reaction (15%), diarrhea (10%), and hypophosphatemia (12%). Regarding pharmacokinetics, area under the curve (AUC) of irinotecan was significantly higher in cycle 2 (following regorafenib dosing) than in cycle 1 (before regorafenib dosing); the ratio of AUC values (cycle 2:cycle 1) was 1.28 (90% confidence interval [CI] 1.06 –1.54). Cmax of irinotecan was only slightly increased, and t½ was unchanged. For SN–38, AUC was significantly higher in cycle 2 than in cycle 1 (ratio 1.44, 90% CI 1.12–1.85), while Cmax was unchanged. In line with the known elimination pathways of platinum and 5-fluorouracil, no pharmacokinetic interaction with regorafenib was seen (10). The study from O'Neil et al. (11) was designed to show whether the addition of regorafenib to FOLFIRI improves PFS (over a placebo-FOLFIRI arm) when given as second-line therapy for patients treated initially with oxaliplatin and fluoropyrimidine-based therapy. The regorafenib/FOLFIRI schedule that was used was the one proposed by Schultheis et al. (10) (i.e. standard FOLFIRI with irinotecan 180 mg/m² plus regorafenib 160 mg daily from day 4 to 10). The study met its primary endpoint of demonstrating that the addition of regorafenib to FOLFIRI prolongs PFS compared to FOLFIRI alone with a HR of 0.72. When looking at tumor response, authors found that regorafenib (combined to chemo) provided more partial responses than placebo plus chemo (35% vs. 19%, p= 0.045). The combination was very tolerable, with little increase in toxicity compared to the control chemotherapy regimen. Of note, regarding the top-3 reported severe (gr. 3-4) AEs, neutropenia, diarrhea, and hypophosphatemia were reported in 41%, 15%, and 14% of the patients, respectively (as compared to 30%, 5%, and 0% in the placebo group) (11). Actually, there is room to combine regorafenib with a chemo triplet such as FOLFIRINOX (5-fluorouracil, irinotecan, oxaliplatin) on the following conditions: controlling patients on UGT1A polymorphisms (at least UGT1A1), stepwise dose-escalation of irinotecan and regorafenib, mandatory granulocyte growth-factor injections.
STUDY OBJECTIVES	**Primary objectives** **Phase I:** To determine the maximum tolerated dose (MTD) and the recommended phase II dose (RP2D), based on the Dose Limiting Toxicities (DLT) of the combination evaluated during the three first cycles following initiation of therapy (observational period), To evaluate the safety profile of the combination **Phase II :** To evaluate the efficacy (48-week disease-control rate) of the study combination.

Secondary objectives

These apply to phase II part of the project.

They include the following evaluations:

- Safety of combination (NCI-CTC v5, neurotoxicity being also evaluated with the Levi's scale),
- Overall response rate and disease control rate according to RECIST 1.1,
- Duration of response in patients who were not operated on for their metastases,
- 8-weeks response rate according to RECIST 1.1,
- Deepness of response,
- Resectability (R0-R1) and unresectability rates (including R2) among patients with liver-only metastases,
- Progression-free survival,
- Progression-free survival since maintenance therapy onset with regorafenib,
- Overall survival.

As translational studies:

- Impact of DDR1 kinase activity on response, PFS and progression-free survival since maintenance therapy onset with regorafenib, and study of the variation of DDR1 activity in patients whom liver mets are deemed resectable,
- Select a population of mCRC with RAS-mutant cfDNA (already done in the PANIRINOX trial)
- Describe the distribution of baseline genotype(s) of RAS-mutant cfDNA
- Monitor the RAS mutant-allele concentration along FOLFIRINOX-R therapy
- Correlate the baseline RAS mutant-allele concentration and the deepness of decrease of this concentration during FOLFIRINOX-R with PFS and with the progression-free survival since maintenance therapy onset with regorafenib.

Primary endpoint:

Phase I: Adverse events as graded using the common toxicity criteria from the NCI-CTCAE v5 and incidence rates of DLT at each dose level during the 3 first cycles of combination therapy.

Dose-limiting toxicities (DLT) will be defined as the occurrence of one or more of the following drug-related toxicities **during the three first cycles of treatment**:

1. **Missing >7 days daily doses of regorafenib due to drug-related toxicity (scheduled treatment pause of regorafenib will not be counted),**

STUDY ENDPOINTS	**2. <u>Non-Hematologic DLT</u>:** ➢ Grade ≥ 3 (CTCAE v5) non-hematologic toxicity, except: -Grade 3 nausea, vomiting, diarrhea, and Grade 2 alopecia -any untreated HFSR that can be adequately controlled with medical intervention, -Grade ≥ 3 lipase elevation without signs of pancreatitis, ➢ Grade ≥ 2 posterior reversible encephalopathy syndrome (PRES), ➢ Grade ≥ 2 retinopathy, ➢ Liver-specific DLTs are: -Drug-related gr. 3-4 bilirubin increase -Drug-related gr. 3-4 AST and/or ALT increase -Drug-related AST and/or ALT increase > 3 x ULN and associated with concurrent bilirubin increase(> 2 x ULN) **3. <u>Hematologic DLT:</u>** ➢ Grade 4 (NCI-CTCAE v5) neutropenia lasting > 3 days, ➢ Grade 3 Febrile neutropenia (ANC < 1,000/mm^3 with fever ≥ 38.5 °C) (NCI-CTCAE v5), ➢ Grade 4 Febrile neutropenia (life-threatening consequences; urgent intervention indicated), ➢ Grade 4 (NCI-CTCAE v5) anemia (i.e. life threatening consequences; urgent intervention indicated), ➢ Platelets <25,000 /mm^3 or platelets < 50,000 /mm^3 associated with bleeding, ➢ INR or PTT elevation of Grade ≥ 3 (NCI-CTCAE v5) with associated bleeding, ➢ Grade ≥ 3 hemorrhage/bleeding events (NCI-CTCAE v5). **Phase II**: 48-week disease-control rate (defined as the rate of non-progressing patients after central review, at 48-week post-initiation of therapy, to all treated patients. **<u>Secondary endpoints</u>:** **Phase II :** Progression-free survival (PFS), defined as the time from date of inclusion to date of first observed disease progression (investigator's radiological or clinical assessment) or death due to any cause, if death occurs before progression is documented. . A central review of CT-scans is planned for patients found progression-free at 48 weeks**.** Patients without tumor progression or death at the time of analysis will be censored at their last date of tumor assessment,

- Disease control rate (DCR), defined as the rate of patients with non progressive disease (i.e., CR, PR or SD), to all included patients,

- Objective response rate (ORR), defined as the rate of patients with CR or PR, to all included patients,

- Deepness of response (DpR) is defined as the relative change in the sum of longest diameters of RECIST target lesions at the nadir, in the absence of new lesions or progression of non-target lesions, as compared to baseline,

- Time to recurrence under maintenance, defined as the time (days) from date of chemotherapy discontinuation (for protocolar reasons) and regorafenib continuation (as maintenance treatment) to date of first observed disease progression (investigator's radiological or clinical assessment) or death due to any cause, if death occurs before progression is documented. Patients without tumor progression or death at the time of analysis will be censored at their last date of tumor assessment,

- Overall survival (OS), defined as the time (months) from date of inclusion to date of death. Patients lost for follow-up at the time of analysis will be censored at their last news,

- Resection (R) rates: R relates to resection margins. R0/R1 are classified by the pathologist and R2 is classified by the surgeon. R0 is defined as the absence of cancer cells seen microscopically at the resection margin. R1 is defined as the presence of cancer cells microscopically at the resection margin (microscopic positive margin). R2 is defined at gross examination with the presence of tumor tissue at the resection margin.
  Resectability rate (R0R1) and non-resectability rate (including R2) among patients with liver-only metastases

As translational studies:

- Central determination of cfDNA levels at baseline, every 8 weeks during treatment and at the end of treatment.
  Impact of DDR1 kinase activity on response and PFS, and study of the variation of DDR1 activity in patients whom liver mets are deemed resectable.

Safety endpoints:

- All AEs occurring after the patient has signed the informed consent until the end of the safety follow-up period (30 days after the end of study therapy) will be documented. This

	• includes any clinical reactions or symptoms reported by the patient or observed by the investigator at the visits, but also any test abnormalities considered clinically relevant by the investigator, • This will be done by the means of physical examinations, measurements of vital signs, ECG recording, and laboratory assessments, • All AE documentation will be event-based (using NCI-CTCAE V5 guidelines), • All AEs that will be ongoing at the end of treatment, will be reviewed and updated up to at least 30 days after stopping the study treatment. They should be followed until resolution or stabilization unless, in the investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease.
RISK AND BENEFITS	The risk-benefit balance of the study is evaluated continuously by the ICM Clinical Research Pharmacovigilance Unit and this risk-benefit balance will be discussed in the periodic safety reports. These reports will contain all required regulatory aspects and will be submitted to the competent authorities and independent scientific committee.
ELIGIBILITY CRITERIA	**Eligibility criteria for prescreening** The following criteria must be met at the time of prescreening: 1. Written informed consent for prescreening 2. Prescreening of patients will be performed at the investigators' discretion up to a maximum of 21 days prior to full study screening. Investigators should ensure all patients will be eligible in terms of disease status within this timeframe. 3. Age ≥ 18 years. 4. Histological documentation of adenocarcinoma of the colon or rectum. 5. Synchronous or metachronous metastatic colorectal cancer not amenable to surgical resection with curative intent. 6. No prior therapy for metastatic disease. 7. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1. 8. Life expectancy of at least 3 months. Besides these basic criteria, any criterion as outlined below under inclusion eligibility criteria for full study and exclusion criteria, already known to prohibit the patient's participation in the study should be

considered. No study-related procedures will be performed that are not covered by the prescreening informed consent form.

Eligibility criteria for full study

Inclusion criteria

1. Written informed consent for full study.
2. Documentation of tumor *RAS* mutation, wild-type homozygous, heterozygous status of *UGT1A1 gene*. *The status of UGT1A1 gene will be* performed by the laboratory chosen by the investigator (for information, appendix 1).
3. Serum uracile < 16 ng/ml
4. Measurable disease, defined as at least one unidimensional measurable lesion on a CT scan, according to RECIST version 1.1.
5. ECOG performance status ≤1.
6. Life expectancy of at least 3 months.
7. Adequate bone marrow, renal and liver functions as evidenced by the following laboratory requirements within
   7 days prior to study treatment initiation:
   a. Absolute neutrophil count (ANC) ≥ 1,500/ mm3 without biologic response modifiers such as granulocyte colony-stimulating factor (G-CSF),
      within 21 days before the start of study treatment,
   b. Platelet count ≥ 100 000/mm3 , without platelet transfusion within 21 days before the start of study treatment,
   c. Hemoglobin (Hb) ≥ 9 g/dL, without blood transfusion or erythropoietin, within 21 days before the start of study treatment,
   d. Serum creatinine ≤ 1.5 x upper limit of normal(ULN)
   e. Serum calcium ≥ LLN and ≤ 1.2 x UNL ; Serum magnesium ≥ LLN and ≤ 1.2 x UNL ; Kalemia ≥ LLN,
   f. Glomerular filtration rate as assessed by the estimated glomerular filtration rate (eGFR) ≥ 50 mL/min per 1.73

m2 calculated by the Modification of Diet in Renal Disease (MDRD) abbreviated formula,

g. Total bilirubin ≤ 1.5 x ULN,

h. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 x ULN (≤ 5 x ULN for patients with liver involvement of their cancer),

i. Alkaline phosphatase (ALP) ≤ 2.5 x ULN (≤ 5.0 x ULN for patients with liver involvement for their cancer and/or bone metastases).

8. Lipase ≤ 1.5 x ULN.
9. Adequate coagulation, as assessed by the following laboratory test results:
   a. International normalized ratio (INR) ≤ 1.5 or prothrombin time (PT) ≤ 1.5 x ULN,
   b. Partial thromboplastin time (PTT) or activated PTT (aPTT) ≤ 1.5 x ULN,

   Note: Patients on stable dose (dose has not been changed in at least 28 days) of anticoagulation therapy will be allowed to participate if they have no sign of bleeding or clotting and INR / PT and PTT / aPTT test results are compatible with the acceptable benefit-risk ratio at the investigator's discretion. In such case, limits as noted would not apply.
10. For women of reproductive potential, negative serum beta human chorionic gonadotropin (β-HCG) pregnancy test obtained within 7 days before the start of study treatment. Women not of reproductive potential are female patients who are postmenopausal or permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy).
11. For women of childbearing potential and men, agreement to use an adequate contraception for the duration of study participation and up to 4 months following completion of therapy for women and 6 months for male patients. Females of childbearing potential who are sexually active with a non-

sterilized male partner must use 2 methods of effective contraception. The investigator or a designated associate is requested to advise the patient on how to achieve an adequate birth control.

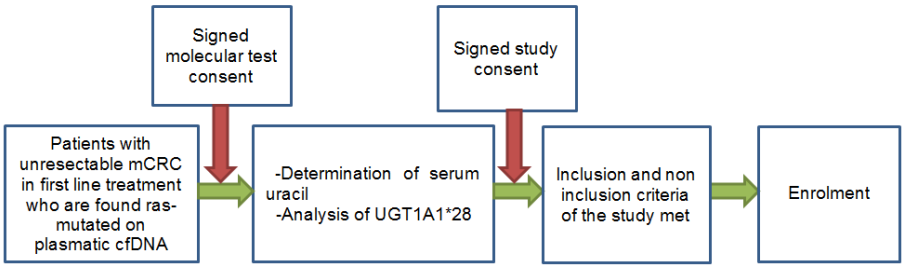
Adequate contraception is defined in the study as any medically recommended method (or combination of methods) as per standard of care.

12. Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests and other study procedures.
13. Affiliation to the Social Security System.

Non-inclusion criteria

1. Previous or concurrent cancer that is distinct in primary site or histology from colorectal cancer within 5 years prior to study inclusion, except for curatively treated cervical cancer in situ, non-melanoma skin cancer and superficial bladder tumors [Ta (non invasive tumor), Tis (carcinoma in situ) and T1 (lamina propria invasion)].
2. Discovery of metastases within 6 months after the termination of adjuvant chemotherapy.
3. Previous treatment for metastatic disease.
   Radiotherapy within 28 days prior to first dose of treatment.
4. Active cardiac disease including any of the following:
   a. Congestive heart failure ≥ New York Heart Association (NYHA) class 2,
   b. Unstable angina (angina symptoms at rest), new-onset angina (begun within the last 3 months),
   c. Myocardial infarction less than 6 months before first dose of treatment,
   d. Cardiac arrhythmias requiring anti-arrhythmic therapy (beta blockers or digoxin are permitted).

5. ECG with a QT/QTc interval higher than 450 ms for men and higher than 470 ms for women Uncontrolled hypertension.
6. Uncontrolled hypertension. (Systolic blood pressure > 140 mmHg or diastolic pressure > 90 mmHg despite optimal medical management).
7. Arterial or venous thrombotic or embolic events such as cerebrovascular accident (including transient ischemic attacks), deep vein thrombosis or pulmonary embolism within 6 months before start of treatment.
8. Persistent proteinuria of National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE V5) grade 3 (i.e. urinary protein ≥ 3.5 g/24 hrs)
9. Peripheral neuropathy > grade1 (NCI-CTCAE v5).
10. Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to first dose of Treatment.
11. Ongoing infection > grade 2 (NCI-CTCAE v5).
12. Known history of human immunodeficiency virus (HIV) infection.
13. Chronic hepatitis B or C infection (if hepatitis status cannot be obtained from medical records, re-testing is required).
14. Seizure disorder requiring medication.
15. Symptomatic metastatic brain or meningeal tumors.
16. Evidence or history of any grade 3-4. Any hemorrhage or bleeding event ≥ grade 3 (NCI-CTCAE v5) within 4 weeks prior to the start of study medication.
17. History of organ allograft.
18. Non-healing wound, ulcer, or bone fracture.
19. Dehydration Grade ≥ 1 NCI-CTCAE v5).
20. Substance abuse, medical, psychological, or social conditions that may interfere with the patient's participation in the study or evaluation of the study results.
21. Known hypersensitivity to any of the study drugs, study drug classes, or any constituent of the products.
22. Interstitial lung disease with ongoing signs and symptoms.

	23. Concomitant intake of St. John's wort. 24. Live attenuated vaccines are prohibited 10 days before the treatment, during the treatment and 3 months after the termination of treatment 25. History of gastrointestinal fistula or perforation 26. Inability to swallow oral medication. 27. Any malabsorption condition. 28. Pregnant or breast-feeding subjects. 29. Any condition that, in the opinion of the investigator, would interfere with the evaluation of study treatment or interpretation of patient safety or study results. 30. Participation in another clinical study with an investigational product during the last 30 days before inclusion. 31. Patients who might be interconnected with or dependent on the sponsor site or the investigator. 32. Legal incapacity or limited legal capacity.
STUDY PRODUCT OR MEDICAL DEVICE	**FOLFIRINOX - REGORAFENIB**
ENROLLMENT PROCEDURE	 • **Phase I part** The phase I part of this study will be designed as a standard 3+3 design for dose escalation/de-escalation and 3 to 6 patients will be enroled in each cohort sequentially, depending on occurrence of dose limiting toxicities.

<table>
<tr>
<td>TREATMENT MODALITIES</td>
<td>
Pre-defined dose levels
<table>
<tr><th>Steps</th><th>Dose Levels</th><th>Number of patients</th></tr>
<tr><td>DL-1</td><td>IRI 150/REGO 80</td><td>0-6</td></tr>
<tr><td>DL1</td><td>IRI 150/REGO 120</td><td>3-6</td></tr>
<tr><td>DL2</td><td>IRI 180/REGO 120</td><td>3-6</td></tr>
<tr><td>DL3</td><td>IRI 180/REGO 160</td><td>3-6</td></tr>
</table>
The 6 patients treated at the RP2D in the phase I part will be included in the phase II part.
Phase I and II:
FOLFIRINOX will be administered as per standard procedures:
every 14 days (1 cycle = 14 days):
Oxaliplatin (Eloxatin® or generic drug): 85mg/m² on day 1, IV infusion over 2 hours, immediately followed by
- Folinic acid 400 mg/m² or Calcium Levofolinate: 200mg/m² given as a 2-hour IV infusion, with the addition, after 30 minutes of
- Irinotecan (Campto® or generic drug) : 150-180 mg/m² as per dose-level given as a 90-minute intravenous infusion through a Y-connector immediately followed by
5-Fluorouracil: 400mg/m² IV bolus then 2400mg/m² over 46 hours continuous infusion.
Prophylactic G-CSF will be systematically given after each course from Day-7 to Day 12.

REGORAFENIB will be given orally at a dose of 80 to 160 mg, as per dose-level, once daily on days 4 to 10 of each cycle

Tumor assessments (computed tomography (CT) or magnetic resonance imaging (MRI)) of the chest, abdomen, pelvis (if patient allergic to iodine contrast agents) will be performed at the baseline, every 8 weeks thereafter.
</td>
</tr>
<tr>
<td>ANCILLARY STUDIES</td>
<td>
Study n°1 : DDR1 activity as a predictor of efficacy of regorafenib
Paraffin-embedded human solid tissue blocks will be sent off at room temperature at the end of the inclusions.
Paraffin-embedded human solid tissue blocks will be returned to the home institution upon completion of ancillary study.
We would like to :
</td>
</tr>
</table>

	1. assess the baseline activity of DDR1 in colorectal samples, 2. to compare the baseline DDR1 activity to the one of patients (actually those who present some degree of tumor shrinkage) who undergo primarily unplanned hepatectomy and let liver metastases available to study, 3. to correlate baseline DDR1 activity to FOLFIRINOX-R efficacy (response rate, PFS, progression-free survival since maintenance therapy onset with regorafenib), 4. to correlate DDR1 activity on resected liver metastases to the time to recurrence. 5. To proceed to the following additional in vitro and in vivo experiments in order to strengthen the importance of DDR1 inhibition provided by regorafenib: ➢ Test the capacity of regorafenib (1-10nM) to inhibit invasive properties of colorectal tumor cells induced by DDR1 overexpression in collagen matrix *in vitro*. ➢ Test in vivo the capacity of regorafenib treatment (10mg/kg) to block metastatic development induced by DDR1 overexpression in colorectal tumor cells that were transplanted in the spleen of nude mice. ➢ **Actually, with this translational research, we aim to assess DDR1 activity as a predictor of efficacy in mCRC patients treated with a regorafenib-based therapy.** **Study n°2 : cfDNA monitoring** Three EDTA tubes will be collected at baseline, every 8 weeks during treatment and at the end of treatment. Because cfDNA analysis has the capacity to reflect tumor load, it could be used to monitor the efficacy of response of mCRC patients to treatment. We aim to better understand the changes of cfDNA concentration along a regorafenib-based therapy.
STATISTICAL CONSIDERATIONS	**Phase I** A minimum of 12 and a maximum of 24 patients will be included. The dose escalation corresponding to a minimum of 3 and a maximum of 6 patients per dose level. A total of 6 patients will be included at the RP2D. **Phase II** With a one-stage Fleming design, α = 5%, β = 20%, p0 (the probability of inefficiency maximum) = 35% and p1 (the probability of minimum efficiency) = 50%, it would be necessary to include 65 evaluable patients (69 patients/ 5% non-evaluable patients). The association can be considered sufficiently effective (reject null hypothesis) if there are at least 29 success (48 weeks disease

STATISTICAL CONSIDERATIONS	control rate = CR / PR / SD) out of 65 evaluable patients, the success rate is significantly greater than 35%. The association can be considered insufficiently effective (rejection of the alternative hypothesis) if there are 28 or less success out of 65 evaluable patients, the success rate is significantly lower than 50%. In total, a maximum of 87 (=18 patients for phase I + 69 patients for phase II including 6 patients treated at the RP2D during the phase I) patients will be included. **<u>Analysis population</u>** Intent To Treat (ITT) population = all included patients. Per-Protocol (PP) population = all eligible patients (patients with no major violations of the inclusion/exclusion criteria) and evaluable patients (included treated patients with evaluation at 48 weeks or without evaluation at 48 weeks if progressive or dead patient). Safety population = all treated patients who received at least one dose of treatment.All statistical analysis will be performed on ITT population, on PP population for efficacy analysis and on Safety population for safety analysis.
STUDY PERIOD	❖ **First inclusion**: april 2019 ❖ **Inclusion period**:12 months Phase I + 12 months Phase II ❖ **End of the inclusion period**: march 2021 ❖ **Expected end of study:** june 2022 ❖ **Report**: september-december 2022 ❖ **Poster/public**: phase I (2020), phase II (april 2023 and july 2023)

1. Background and rationale

Colorectal cancer

Colorectal cancer (CRC) is a major cause of morbidity and mortality globally. More than 50% of patients can be expected to develop metastatic disease, and most of these patients will require palliative systemic therapy. The primary goal for patients who present with technically resectable liver metastases is definitely cure, with R0 resection as the primary goal. However, any patient with limited liver and/or lung metastases should be considered a candidate for potential secondary resection as there are no criteria that allow physicians to distinguish between those patients for whom purely palliative treatment and those or whom potentially curative treatment is appropriate. Although survival times are slightly shorter for patients who undergo conversion therapy followed by surgery than for patients with initially resectable metastatic disease, they are far better than if resection is not carried out at all (1).

As per ESMO guidelines, first-line therapy commonly involves the doublet (2-CT) regimens of 5-fluorouracil, folinic acid, and either oxaliplatin (FOLFOX) or irinotecan (FOLFIRI). The addition of targeted therapies, such as bevacizumab (a pure anti-angiogenic agent which binds circulating VEGF-A), cetuximab, and panitumumab, to FOLFOX or FOLFIRI may be helpful to some patients in improving tumor response and ultimately overall survival. The cytotoxic triplet (3-CT) FOLFOXIRI with or without bevacizumab may be an option in selected fit and motivated patients when cytoreduction (tumour shrinkage) is needed to undergo conversion therapy (1).

RAS-mutated (RAS-mut) mCRC

RAS mutations are found in about 50% of mCRC tumors. As recently rephrased by Modest et al. (2) these mutations exclude affected patients from epidermal growth factor receptor (EGFR)-directed therapy. Besides their negative predictive value, *RAS* mutations may also carry distinct prognostic information. Modest et al. (2) studied the prognosis by *RAS* status of a total of 1239 mCRC patients from five randomized trials studying 2-CT. Actually, PFS and OS were significantly influenced by molecular subgroups. Multivariate comparison of PFS and OS in patients with mutant tumors versus patients with non-mutated tumors revealed a negative prognostic effect of *RAS* mutations. Interestingly, the negative prognostic role of these mutations was consistently observed across different treatment regimens (subgroups of irinotecan- and oxaliplatin-treated patients as well as in bevacizumab- and non-bevacizumab-treated patients). Median PFS and OS were 10.3 vs. 9.5 months and 26.9 vs. 21.1 months in *RAS*-wildtype (and *BRAF*-wildtype) and *RAS*-mut patients, respectively

(2).The TRIBE consortium reported that a 3-CT (FOLFOXIRI) combined with bevacizumab provided a significantly longer PFS (the primary end-point of the study) than did the 2-CT FOLFIRI plus bevacizumab (3, 4). In the subgroup of *RAS*- and *BRAF*-wild-type patients, those in the FOLFOXIRI plus bevacizumab group reported a median PFS of 13.7 months (95%CI, 10.1-18.1) compared with 12.2 months (95%CI, 9.5-14.4) in the FOLFIRI plus bevacizumab group (HR 0.85, 95%CI 0.55-1.3) (4). Later on, the same group reported that FOLFOXIRI plus bevacizumab provided a significantly longer overall survival than the FOLFIRI plus bevacizumab group (HR 0.80, 95%CI 0·65–0·98; p=0·03) (4). Looking at survival by RAS status, Cremolini et al. (4) reported that median OS was 37.1 months (95%CI, 29.7–42.7) in the *RAS*- and *BRAF*-wild-type subgroup compared with 25.6 months (95%CI, 22.4–28.6) in the *RAS*-mut subgroup (HR 1.49, 95%CI, 1.11–1·99). Interestingly, median PFS was 13.7 months (95% CI 10.1–18.1) in the RAS-wild-type subgroup treated with FOLFOXIRI plus bevacizumab, while PFS data were not given for the RAS-mut patients (4). However, it was possible to estimate median PFS (i.e. 9.4 months) from the Kaplan-Meier curve which was provided for these RAS-mut patients (4).

The median PFS to benchmark in *RAS*-mut mCRC is 9.4 months (with FOLFOXIRI plus bevacizumab)

Regorafenib

Regorafenib is a small-molecule inhibitor of multiple membrane-bound and intracellular kinases RET, VEGFR 1, 2, 3, c-Kit, PDGFR-α, β, FGFR1, 2, TIE2, DDR1, DDR2, Trk2A, Eph2A, RAF-1, BRAF, BRAFV600E, SAPK2, PTK5, and Abl. Beyond its well-known antiangiogenic properties, regorafenib has also less-known anti-proliferative activities in human colon cancer cell lines. Interestingly, regorafenib potently inhibits growth of patient-derived CRC xenografts alone and in combination with irinotecan (5-7). Regorafenib is approved for refractory mCRC patients (8), for locally advanced, unresectable or metastatic GIST patients and for HCC patients previously treated with sorafenib. The recommended dose is 160 mg (40 mg × 4 tablets) orally, once daily for the first 21 days of each 28-day cycle. Two phase III trials demonstrated a significant overall survival benefit for regorafenib over placebo in patients with mCRC who progressed on standard therapies (8, 9). Two phase II trials studied the safety and efficacy profile of regorafenib when combined to chemotherapy in patients with mCRC (10, 11). *In vitro* data indicate that both regorafenib and its metabolite M-2 inhibit glucuronidation mediated by UGT1A1 and UGT1A9 (whereas M-5 only inhibits UGT1A1), hence triggering potential pharmacokinetic interactions. The study

from Schultheis et al. (10) was designed to explore whether addition of regorafenib to FOLFOX or FOLFIRI could be feasible as a treatment of mCRC, in terms of safety and pharmacokinetic interactions of the various drug components of the regimen. Forty-five patients were treated every 2 weeks with 5-fluorouracil 400 mg/m² bolus then 2400 mg/m² over 46 h, folinic acid 400 mg/m², and either oxaliplatin 85 mg/m² or irinotecan 180 mg/m². On days 4–10, patients received regorafenib 160 mg orally once daily. Drug-related adverse events resulted in dose modification, dose interruption, or permanent discontinuation of study treatment in 31 (69%) patients overall (18 [72%] FOLFOX and 13 [65%] FOLFIRI). Dose reduction or dose interruption of at least one of the chemotherapy components was observed in 52% of patients treated with FOLFOX and 65% of patients receiving FOLFIRI. A dose reduction of 5-fluorouracil due to AEs was necessary in 18% of administered cycles. 5-Fluorouracil administration was omitted in 8% of cycles. Oxaliplatin and irinotecan doses were reduced in 11% and 12% and interrupted in 11% and 5% of administered cycles, respectively. Actually, regorafenib had acceptable tolerability in combination with chemotherapy. The most frequent grade 3-4 AEs were: neutropenia (45%), Hand-Foot Skin Reaction (15%), diarrhea (10%), and hypophosphatemia (12%). Regarding pharmacokinetics, area under the curve (AUC) of irinotecan was significantly higher in cycle 2 (following regorafenib dosing) than in cycle 1 (before regorafenib dosing); the ratio of AUC values (cycle 2:cycle 1) was 1.28 (90% confidence interval [CI] 1.06 –1.54). C_{max} of irinotecan was only slightly increased, and $t_{½}$ was unchanged. For SN–38, AUC was significantly higher in cycle 2 than in cycle 1 (ratio 1.44, 90% CI 1.12–1.85), while C_{max} was unchanged. In line with the known elimination pathways of platinum and 5-fluorouracil, no pharmacokinetic interaction with regorafenib was seen (10). The study from O'Neil et al. (11) was designed to show whether the addition of regorafenib to FOLFIRI improves PFS (over a placebo-FOLFIRI arm) when given as second-line therapy for patients treated initially with oxaliplatin and fluoropyrimidine-based therapy. The regorafenib/FOLFIRI schedule that was used was the one proposed by Schultheis et al. (10) (i.e. standard FOLFIRI with irinotecan 180 mg/m² plus regorafenib 160 mg daily from day 4 to 10). The study met its primary endpoint of demonstrating that the addition of regorafenib to FOLFIRI prolongs PFS compared to FOLFIRI alone with a HR of 0.72. When looking at tumor response, authors found that regorafenib (combined to chemo) provided more partial responses than placebo plus chemo (35% vs. 19%, p= 0.045). The combination was very tolerable, with little increase in toxicity compared to the control chemotherapy regimen. Of note, regarding the top-3 reported severe (gr. 3-4) AEs, neutropenia, diarrhea, and hypophosphatemia were reported in 41%, 15%,

and 14% of the patients, respectively (as compared to 30%, 5%, and 0% in the placebo group) (11).

- **There is room to combine regorafenib with a chemo triplet such as FOLFIRINOX (5-fluorouracil, irinotecan, oxaliplatin) on the following conditions:** controlling patients on *UGT1A* polymorphisms (at least UGT1A1), stepwise dose-escalation of irinotecan and regorafenib, mandatory granulocyte growth-factor injections.

FOLFIRINOX or FOLFOXIRI: A matter of dose of irinotecan and of 5-fluorouracil.

- **FOLFOXIRI** is a 60-minute infusion of **irinotecan at a dose of 165 mg/m²,** and a 120-minute infusion of oxaliplatin at a dose of 85 mg/m² and a concomitant 120-minute infusion of Leucovorin at a dose of 200 mg/m² followed by a 48-hour continuous infusion of **fluorouracil to a total dose of 3200 mg/m².** Cycles are repeated every 14 days. This regime has been developed by Italian investigators in mCRC (2, 3).
- **FOLFIRINOX** is a 120-minute IV infusion of oxaliplatin at a dose of 85mg/m² on day 1, immediately followed by folinic acid 400 mg/m² (or calcium levofolinate 200 mg/m²) given as a 2-hour IV infusion, with the addition, after 30 minutes, of **irinotecan 180 mg/m²**, given as a 90-minute intravenous infusion through a Y-connector immediately followed by **5-Fluorouracil 400mg/m² IV bolus then 2400mg/m²** over 46 hours continuous infusion. Cycles are repeated every 14 days. This regime has been developed by french investigators in metastatic pancreatic cancer and in mCRC (11, 12).

- **We have selected FOLFIRINOX rather than FOLFOXIRI as a backbone of our experimental treatment because 1) french investigators are used to treat patients with such regimen, and because 2) the FOLFIRI-regorafenib that had been investigated by O'Neil et al (11) used the same irinotecan and 5-fluorouracil doses than the FOLFIRINOX regimen.**

  Why having chosen 48-week disease-control rate, rather than overall response rate as the primary objective of the phase II part of this FOLFIRINOX-R trial (see page 7)? Overall response rate could have been the primary objective of this trial, as we are confident with the postulate that regorafenib is able to induce some additional tumour shrinkage to FOLFIRINOX backbone, but we are also cautious with that hypothesis. However, the 48-week disease-control rate includes not only the effect of

tumor responses that are awaited but also stable disease. In addition, this 48-week data cutoff (i.e.48-week disease-control rate) is also the median PFS (actually, 12.2 months) that had been reported in *RAS*-mut mCRC treated with the FOLFOXIRI-bevacizumab that we want to benchmark. To conclude, we think that the 48-week disease-control rate carries more valuable informations than overall response rate, as it captures the true effect of the addition of regorafenib to FOLFIRINOX.

DDR1 activity as a predictor of efficacy of regorafenib

Serge ROCHE, Ph.D., Centre de Recherche en Biologie cellulaire de Montpellier

Antoine ADENIS, M.D., Ph.D., ICM, IRCM, Montpellier

DDR1 is a tyrosine kinase receptor for collagens, which are major components of CRC microenvironment. DDR1 functions as a central extracellular matrix sensor to regulate cell adhesion and to promote tumor cell invasion and cancer stem cell survival in a collagen rich microenvironment (14, 15). Interestingly, the DDR1 kinase activity seems to be dispensable for several DDR1 functions reported in human cancers (16). Our group recentely reported important DDR1 kinase-dependent function in CRC metastasis formation and also showed that DDR1 inhibition provided significant anti-tumor activity in this cancer (17). Actually, we showed that DDR1 pharmacological inhibition by a potent DDR1 inhibitor (i.e.nilotinib) inhibits the invasive and metastatic behavior of CRC cells through a RAS-independent mechanism. We were able to inhibit the DDR1-mediated metastatic potential of CRC cells in a liver metastasis mouse model and of patient-derived cell lines originating from metastatic tumors and circulating CRC cells. DDR1 inhibition displayed too anti-tumor activity in mice that have already developed DDR1-dependent metastatic nodules, revealing an additional important role of DDR1 activity in metastatic growth (17). Clinical relevance of our findings is further supported by showing that DDR1 expression level is an independent marker of poor prognosis in stage IV patients, and is not correlated with already described variables like tumor location, grade, number of metastatic sites, and CMS transcriptional subtypes. Besides, its relative kinase activity was dramatically increased in CRC metastatic nodules (mean > 10 fold) from a small cohort of patient with mCRC (12/20 patients), when compared to non-transformed tissue or primary tumors of the same patients. This observation is consistent with a DDR1 kinase role in liver metastatic development of CRC patients (17). We thus propose that targeting tumor signaling emanated from the

microenvironment through inhibition of DDR1 activity could be an effective strategy to treat mCRC.

Interestingly, regorafenib is also a potent inhibitor of DDR1 (as well as its M2 and M5 metabolites), with a *Kd* identified (0.9 nmol/L) as the lowest of all the kinases being inhibited (18). Based on our previous experience with another DDR1 inhibitor, we postulate that the antioncogenic properties of regorafenib (as opposed to its inhibitory properties against various stromal and angiogenic targets) are mainly driven by DDR1 inhibition.

Taking avantage of the present FOLFIRINOX-R trial, we would like to:

1. assess the baseline activity of DDR1 in colorectal samples,
2. to compare the baseline DDR1 activity to the one of patients (actually those who present some degree of tumor shrinkage) who undergo primarily unplanned hepatectomy and let liver metastases available to study,
3. to correlate baseline DDR1 activity to FOLFIRINOX-R efficacy (response rate, PFS, progression-free survival since maintenance therapy onset with regorafenib),
4. to correlate DDR1 activity on resected liver metastases to the time to recurrence.
5. To proceed to the following additional *in vitro* and *in vivo* experiments in order to strengthen the importance of DDR1 inhibition provided by regorafenib:
   - Test the capacity of regorafenib (1-10nM) to inhibit invasive properties of colorectal tumor cells induced by DDR1 overexpression in collagen matrix *in vitro*.
   - Test *in vivo* the capacity of regorafenib treatment (10mg/kg) to block metastatic development induced by DDR1 overexpression in colorectal tumor cells that were transplanted in the spleen of nude mice.

➢ **Actually, with this translational research, we aim to assess DDR1 activity as a predictor of efficacy in mCRC patients treated with a regorafenib-based therapy.**

Expected results: Our hypothesis is that a high DDR1 kinase activity level is associated with a shorter PFS/OS in patients with CRC, as already reported at the DDR1 transcript level and suggested on DDR1 activity from a small cohort of patients with metastatic CRC (17). Based on the metastatic function of DDR1 in CRC, the level of DDR1 activity may be a marker of its metastatic function in patient tumor samples. Regorafenib may reduce metastatic growth in "DDR1 high" CRC and a correlation is expected between high DDR1 tumor activity and tumor response to regorafenib. We also predict that, due to the high affinity of regorafenib to

DDR1, this kinase inhibitor may block all DDR1 invasive/metastatic activities in CRC experimental models described above.

cfDNA monitoring

- Alain Thierry, Ph.D., Institut de Recherche sur le Cancer de Montpellier (IRCM)
- Antoine Adenis, M.D., Ph.D., ICM, IRCM
- Marc Ychou, M.D., Ph.D., ICM, IRCM

Our group developed a Q-PCR based-method (Intplex) which is a mutation targeted test that enables rapid, highly sensitive, cost effective and repetitive analysis (19, 20). We carried out the first clinical validation of cfDNA analysis in oncology, i.e. in colorectal cancer (21) using this test. Thus, we performed a blinded prospective multicenter study to compare *KRAS* and *BRAF* mutation status data obtained from the analysis of tumor tissue by routine gold-standard methods and of plasma DNA from mCRC patients before initiation of anti-EGFR therapy. The mutation status was determined by both methods from 106 patient samples. cfDNA analysis showed 100% specificity and sensitivity for the *BRAF V600E* mutation. For the seven tested *KRAS* point mutations, the method exhibited 98% specificity and 92% sensitivity with a concordance value of 96%. Mutation load, expressed as the proportion of mutant alleles in cfDNA, was highly variable (0.5–64.1%, median 10.5%) among mutated samples. CfDNA was detected in 100% of patients with mCRC. This study carried out under the most stringent criteria for determining performance of a diagnostic test (STARD criteria) shows that liquid biopsy through cfDNA analysis could advantageously replace tumor-section analysis and expand the scope of personalized medicine for patients with cancer (21, 22).Considering the results we accumulated, works from other groups, clinical use of cfDNA analysis in general or in the context of the selection of mCRC patients toward targeted therapy is warranted in the coming years.

In this context, we are currently investigating, within the PANIRINOX trial (sponsor: UNICANCER), the clinical efficacy reached with an intensified regimen combining FOLFIRINOX plus panitumumab in mCRC patients with *RAS* wild-type status determined by cfDNA analysis in comparison with the standard treatment ofFOLFOX6 plus panitumumab (23).

- **Considering this active screening of mCRC patients with *RAS* wild-type cfDNA, we have an obvious opportunity to select for research purpose, mCRC patients with *RAS*-mutant cfDNA.**

Because cfDNA analysis has the capacity to reflect tumor load, it has also been used to monitor the efficacy of response of mCRC patients to treatment, in a few retrospective series with a small number of patients (24-26)

- **Actually, with this translational research, we aim to better understand the changes of *RAS*-mutant cfDNA concentration along a regorafenib-based therapy**

2. Study objectives and Endpoints

2.1 Objectives

2.1.1 Primary objectives

Phase I:

-To determine the maximum tolerated dose (MTD) and the recommended phase II dose (RP2D), based on the Dose Limiting Toxicities (DLT) of the combination evaluated during the three first cycles following initiation of therapy (observational period)

-To evaluate the safety profile of the combination.

Phase II: To evaluate the efficacy (48-week disease-control rate) of study combination

2.1.2 Secondary objective

These apply to phase II part of the project.

They include the following evaluations:

- Safety of combination (NCI-CTC v5, neurotoxicity being also evaluated with the Levi's scale – appendix 2)
- Overall response rate and disease control rate according to RECIST 1.1
- Duration of response in patients who were not operated on for their metastases
- Study of variations in the concentration of Ras-mutant cfDNA during treatment,
- 8-weeks response rate according to RECIST 1.1
- Deepness of response

- Resectability (R0,R1) and unresectability rates (including R2) among patients with liver-only metastases
- Progression-free survival
- Progression-free survival since maintenance therapy onset with regorafenib
- Overall survival

As translational studies:

- Impact of DDR1 kinase activity on response, PFS and progression-free survival since maintenance therapy onset with regorafenib, and study of the variation of DDR1 activity in patients whom liver mets are deemed resectable.
- Select a population of mCRC with *RAS*-mutant cfDNA (already done in the PANIRINOX trial)
- Describe the distribution of baseline genotype(s) of RAS-mutant cfDNA
- Monitor the *RAS* mutant-allele concentration along FOLFIRINOX-R therapy
- Correlate the baseline RAS mutant-allele concentration and the deepness of decrease of this concentration during FOLFIRINOX-R with PFS and with the progression-free survival since maintenance therapy onset with regorafenib.

2.2 Endpoints

2.2.1 Primary endpoint

Phase I: Adverse events as graded using the common toxicity criteria from the NCI-CTCAE V5 and incidence rates of DLT at each dose level during the 3 first cycles of combination therapy,

Dose-limiting toxicities (DLT) are defined as the occurrence of one or more of the following drug-related toxicities during the three fist cycles of treatment:

Non-Hematologic DLT:

- Missing > 7 days daily doses of regorafenib due to drug-related toxicity (scheduled treatment pause of regorafenib will not be counted),
- Grade ≥ 3 (NCI-CTCAE V5) non-hematologic toxicity, except:
  -Grade 3 nausea, vomiting, diarrhea and grade 2 alopecia
  -any untreated HFSR that can be adequately controlled with medical intervention,
  -Grade ≥ 3 lipase elevation without signs of pancreatitis,

- Grade ≥ 2 posterior reversible encephalopathy syndrome (PRES),
- Grade ≥ 2 retinopathy,
- Liver-specific DLTs are:

  -Drug-related gr. 3-4 bilirubin increase
  -Drug-related gr. 3-4 AST and/or ALT increase
  -Drug-related AST and/or ALT increase > 3 x ULN and associated with concurrent bilirubin increase(> 2 x ULN)

Hematologic DLT:

- Grade 4 (NCI-CTCAE V5) neutropenia lasting > 3 days,
- Febrile neutropenia Grade 3 (ANC < 1,000/mm3 with fever ≥ 38.5 °C) (CTCAE V5),
- Febrile neutropenia Grade 4 (life-threatening consequences; urgent intervention indicated),
- Grade 4 (NCI-CTCAE V5) anemia (i.e life-threatening consequences; urgent intervention indicated),
- Platelets < 25 000 /mm3 or platelets < 50 000 /mm3 associated with bleeding,
- INR or PTT elevation of Grade ≥ 3 (NCI-CTCAE V5) with associated bleeding,
- Grade ≥ 3 hemorrhage/bleeding events (NCI-CTCAE V5).

Phase II: 48-week disease-control rate (defined as the rate of non-progressing patients after central review, at 48-week post-initiation of therapy, to all treated patients.

Treated patients who have progressed or died before the 48-week evaluation will be considered as failure.

2.2.2 Secondary endpoints

- Progression-free survival (PFS), defined as the time from date of inclusion to date of first observed disease progression (investigator's radiological or clinical assessment) or death due to any cause, if death occurs before progression is documented. A central review of CT-scans is planned for patients found progression-free at 48 weeks**.** Patients without tumor progression or death at the time of analysis will be censored at their last date of tumor assessment.
- Disease control rate (DCR), defined as the rate of patients with non-progressive disease (i.e., CR, PR or SD), to all includes patients.

- Objective response rate (ORR), defined as the rate of patients with CR or PR, to all patients included.
- Deepness of response (DpR) is defined as the relative change in the sum of longest diameters of RECIST target lesions at the nadir, in the absence of new lesions or progression of non-target lesions, as compared to baseline.
- Time to recurrence under maintenance, defined as the time (days) from date of chemotherapy discontinuation (for protocolar reasons) and regorafenib continuation (as maintenance treatment) to date of first observed disease progression (investigator's radiological or clinical assessment) or death due to any cause, if death occurs before progression is documented. Patients without tumor progression or death at the time of analysis will be censored at their last date of tumor assessment.
- Overall survival (OS), defined as the time (months) from date of inclusion to date of death. Patients lost for follow-up at the time of analysis will be censored at their last news.
- Resection (R) rates: R relates to resection margins. R0/R1 are classified by the pathologist and R2 is classified by the surgeon. R0 is defined as the absence of cancer cells seen microscopically at the resection margin. R1 is defined as the presence of cancer cells microscopically at the resection margin (microscopic positive margin). R2 is defined at gross examination with the presence of tumor tissue at the resection margin.

  Resectability rate (R0R1) and unresectability rate (including R2) among patients with liver-only metastases.

As translational studies:

- Central determination of cfDNA levels at baseline, every 8 weeks during treatment and at the end of treatment.
- Impact of DDR1 kinase activity on response and PFS, and study of the variation of DDR1 activity in patients whom liver metastases are deemed resectable.

3. Experimental plan

3.1 Study design

This will be a prospective, Interventional, multicenter, open-label, uncontrolled phase I/II trial. 87 (18 phase I and 69 phase II including 6 patients treated at the RP2D during the phase I) patients will be included in several centers.

Phase I

DLT monitoring must be performed during the first three cycles of treatment. Patients will be treated until disease progression.
In case of patient withdrawal before completing the entire third cycle for reasons other than DLT, a new patient will be included at this dose level.

The phase I part of this study will be designed as a standard 3+3 design for dose escalation/de-escalation and 3 to 6 patients will be enrolled in each cohort sequentially, depending on occurrence of dose limiting toxicities (Figure 1).

A standard 3 + 3 design will be followed in the dose escalation part of study.
Three dose levels for Irinotecan/Regorafenib (IRI 150/REGO 120, IRI 180/REGO 120, IRI 180/REGO 160) are planned as well as a -1 level (IRI 150/REGO 80) to be opened in case of maximum tolerated dose (MTD) was reached at level 1 (Table 1).

Table 1 :

Steps	Dose Levels	Number of patients
DL-1	IRI 150/REGO 80	0-6
DL1	IRI 150/REGO 120	3-6
DL2	IRI 180/REGO 120	3-6
DL3	IRI 180/REGO 160	3-6

At each dose level, three patients will be included. Three additional patients will be enrolled at the same dose level if one dose limiting toxicity (DLT) is observed in the first three patients of this dose level (Figure 1).

Figure 1 :

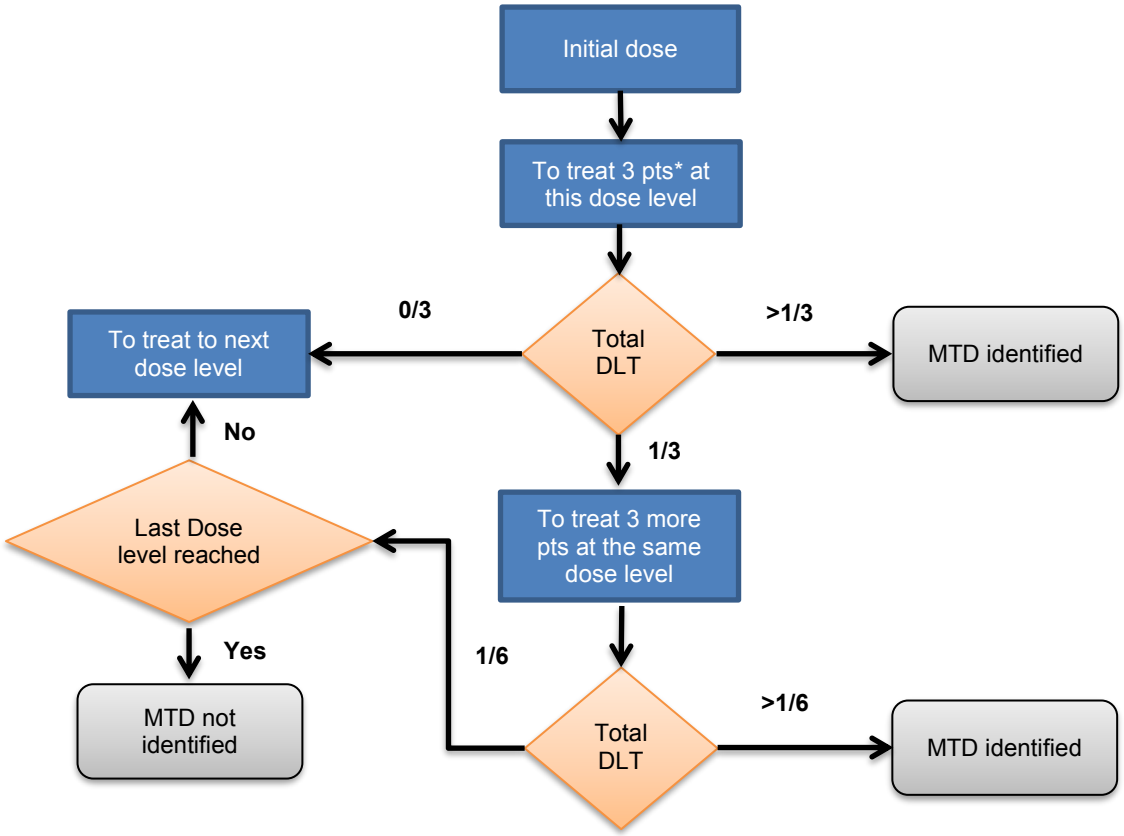


Table 2 : Dose escalation rules

Outcome (# DLT / # Patients)	Action
0 DLT out of the first 3 patients	Include 3 patients at the next dose level
1 DLT out of 3 patients	Include 3 additional patients at the same dose level.
≥ 2 DLT out of 3 patients	Stop dose escalation. Include 3 additional patients at the previous dose level (unless 6 subjects were already treated).
≥ 2 DLT out of 6 patients	Stop dose escalation. Include 3 additional patients at the previous dose level (unless 6 patients were already treated).

The MTD is defined as the dose at which at least two out of three to six patients experienced a DLT during the first three cycles of treatment.

Dose escalation will be stopped if MTD is reached or the last dose level (IRI 180/REGO 160) is reached (MTD not reached).

The recommended phase II dose (RP2D) is defined as the dose closest to the MTD at which a DLT is observed in 0/3 or 1/6 patients.

Should any patient discontinue the study prior to completing the entire (3 cycles) for reasons other than a DLT then a replacement patient will be added at that dose level.

DLT recording and assessment

- Study sites will document any DLT immediately and report a DLT event to the Sponsor within 24 hours of site's awareness.
- Once recruitment of 3 or 6 patients per dose level has been completed, recruitment will be halted by default until the 3-cycle dose-finding treatment has been completed for each patient and sites have reported all relevant safety findings.
- The decision to stop, modify or continue escalation will be made by the project team (coordinator, statistician, project manager, safety vigilance head and vigilance manager) if there are no SUSARs. In the event of SUSARs, we will refer the matter to the independent scientific committee.
- The Sponsor will communicate further dosage information (dose escalation or de-escalation) and additional safety measures to all participating sites/investigators.

Phase II :

The 6 patients treated at the RP2D in the phase I part will be included in the phase II part.

The multicenter, phase II trial is planned to enroll 69 patients. The patients who meet the study eligibility criteria will be included to receive the study drug.

- **First inclusion**: april 2019
- **Inclusion period**:12 months Phase I + 12 months Phase II
- **End of the inclusion period**: march 2021
- **Expected end of study:** june 2022
- **Report**: september-december 2022
- **Poster/public:** phase I (2020), phase II (april 2023 and july 2023)

3.2 Study period

3.3 Compensation modalities

The sponsor maintains clinical trial insurance coverage for this study in accordance with the laws and regulations of the country in which the study is performed.

4. Population

4.1 Number of planned patients

-87 patients included out of approximately 174 screened patients.

4.2 Inclusion criteria

Eligibility criteria for prescreening

The following criteria must be met at the time of prescreening:

1. Written informed consent for prescreening.
2. Prescreening of patients will be performed at the investigators' discretion up to a maximum of 21 days prior to full study screening. Investigators should ensure all patients will be eligible in terms of disease status within this timeframe.
3. Age ≥18 years.
4. Histological documentation of adenocarcinoma of the colon or rectum.
5. Synchronous or metachronous metastatic colorectal cancer not amenable to surgical resection with curative intent.
6. No prior therapy for metastatic disease.
7. Eastern Cooperative Oncology Group (ECOG) performance status ≤1.
8. Life expectancy of at least 3 months.

Besides these basic criteria, any criterion as outlined below under inclusion eligibility criteria for full study and exclusion criteria, already known to prohibit the patient's participation in the study should be considered. No study-related procedures will be performed that are not covered by the prescreening informed consent form.

Eligibility criteria for full study

1. Written informed consent for full study
2. Documentation of tumor *RAS* mutation, wild-type homozygous, heterozygous status of *UGT1A1 gene*. *The status of UGT1A1 gene will be* performed by the laboratory chosen by the investigator (for information, appendix 1).
3. Serum uracile < 16 ng/ml
4. Measurable disease, defined as at least one unidimensional measurable lesion on a CT scan, according to RECIST version 1.1.
5. ECOG performance status ≤1.
6. Life expectancy of at least 3 months.

7. Adequate bone marrow, renal and liver functions as evidenced by the following laboratory requirements within 7 days prior to study treatment initiation:
    a. Absolute neutrophil count (ANC) ≥ 1 500/ mm^3 without biologic response modifiers such as granulocyte colony-stimulating factor (G-CSF), within 21 days before the start of study treatment,
    b. Platelet count ≥ 100 000/mm^3 , without platelet transfusion within 21 days before the start of study treatment,
    c. Hemoglobin (Hb) ≥ 9 g/dL, without blood transfusion or erythropoietin within 21 days before the start of study treatment,
    d. Serum creatinine ≤ 1.5 x upper limit of normal (ULN),
    e. Serum calcium ≥ LLN and ≤ 1.2 x UNL ; Serum magnesium ≥ LLN and ≤ 1.2 x UNL ; Kalemia ≥ LLN,
    f. Glomerular filtration rate as assessed by the estimated glomerular filtration rate (eGFR) ≥ 50 mL/min per 1.73 m^2 calculated by the Modification of Diet in Renal Disease (MDRD) abbreviated formula,
    g. Total bilirubin ≤ 1.5 x ULN,
    h. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 x ULN (≤ 5 x ULN for patients with liver involvement of their cancer),
    i. Alkaline phosphatase (ALP) ≤ 2.5 x ULN (≤ 5.0 x ULN for patients with liver involvement for their cancer and/or bone metastases).
8. Lipase ≤1.5 x ULN.
9. Adequate coagulation, as assessed by the following laboratory test results:
    c. International normalized ratio (INR) ≤ 1.5 or prothrombin time (PT) ≤ 1.5 x ULN,
    d. Partial thromboplastin time (PTT) or activated PTT (aPTT) ≤ 1.5 x ULN,
    Note: Patients on stable dose (dose has not been changed in at least 28 days) of anticoagulation therapy will be allowed to participate if they have no sign of bleeding or clotting and INR / PT and PTT / aPTT test results are compatible with the acceptable benefit-risk ratio at the investigator's discretion. In such case, limits as noted would not apply.
10. For women of reproductive potential, negative serum beta human chorionic gonadotropin (β-HCG) pregnancy test obtained within 7 days before the start of study treatment.

Women not of reproductive potential are female patients who are postmenopausal or permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy).

11. For women of childbearing potential and men, agreement to use an adequate contraception for the duration of study participation and up to 4 months following completion of therapy for women and 6 months for male patients. Females of childbearing potential who are sexually active with a non-sterilized male partner must use 2 methods of effective contraception. The investigator or a designated associate is requested to advise the patient on how to achieve an adequate birth control. Adequate contraception is defined in the study as any medically recommended method (or combination of methods) as per standard of care.
12. Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests and other study procedures.
13. Affiliation to the Social Security System.

4.3 Non-inclusion criteria

1. Previous or concurrent cancer that is distinct in primary site or histology from colorectal cancer within 5 years prior to study inclusion, except for curatively treated cervical cancer in situ, non-melanoma skin cancer and superficial bladder tumors [Ta (non invasive tumor), Tis (carcinoma in situ) and T1 (lamina propria invasion)].
2. Discovery of metastases within 6 months after the termination of adjuvant chemotherapy.
3. Previous treatment for metastatic disease.
4. Radiotherapy within 28 days prior to first dose of treatment.
5. Active cardiac disease including any of the following:
    a. Congestive heart failure ≥ New York Heart Association (NYHA) class 2 (appendix 3),
    b. Unstable angina (angina symptoms at rest), new-onset angina (begun within the last 3 months),
    c. Myocardial infarction less than 6 months before first dose of treatment,
    d. Cardiac arrhythmias requiring anti-arrhythmic therapy (beta blockers or digoxin are permitted).
6. ECG with a QT/QTc interval higher than 450 ms for men and higher than 470 ms for women.

7. Uncontrolled hypertension. (Systolic blood pressure > 140 mmHg or diastolic pressure > 90 mmHg despite optimal medical management).
8. Arterial or venous thrombotic or embolic events such as cerebrovascular accident (including transient ischemic attacks), deep vein thrombosis or pulmonary embolism within 6 months before start of treatment.
9. Persistent proteinuria of National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE V5) grade 3 (i.e. urinary protein ≥ 3.5 g/24 hrs)
10. Peripheral neuropathy > grade1 (NCI-CTCAE v5).
11. Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to first dose of treatment.
12. Ongoing infection > grade 2 (NCI-CTCAE v5).
13. Known history of human immunodeficiency virus (HIV) infection.
14. Chronic hepatitis B or C infection (if hepatitis status cannot be obtained from medical records, re-testing is required).
15. Seizure disorder requiring medication.
16. Symptomatic metastatic brain or meningeal tumors.
17. Evidence or history of any grade 3-4 bleeding diathesis. Any hemorrhage or bleeding event ≥ Grade 3 (NCI-CTCAE v5) within 4 weeks prior to the start of study medication.
18. History of organ allograft.
19. Non-healing wound, ulcer, or bone fracture.
20. Dehydration Grade ≥ 1 (NCI-CTCAE v5).
21. Substance abuse, medical, psychological, or social conditions that may interfere with the patient's participation in the study or evaluation of the study results.
22. Known hypersensitivity to any of the study drugs, study drug classes, or any constituent of the products.
23. Interstitial lung disease with ongoing signs and symptoms.
24. Concomitant intake of St. John's wort.
25. Live attenuated vaccines are prohibited 10 days before the treatment, during the treatment and 3 months after the termination of treatment
26. History of gastrointestinal fistula or perforation
27. Inability to swallow oral medication.
28. Any malabsorption condition.
29. Pregnant or breast-feeding subjects.

30. Any condition that, in the opinion of the investigator, would interfere with the evaluation of study treatment or interpretation of patient safety or study results.
31. Participation in another clinical study with an investigational product during the last 30 days before inclusion.
32. Patients who might be interconnected with or dependent on the sponsor site or the investigator.
33. Legal incapacity or limited legal capacity.

4.4 Procedure

Before the inclusion of the patient in the study, the investigator must verify :

-that the screening inclusion and non-inclusion criteria have been met

-that the molecular test consent has been obtained.

There's no paper form for this step and no registering.

Inclusion:

The inclusion request will be performed **by fax for phase I**. After the consent form has been signed and all inclusion/ non-inclusion criteria have been met, the investigator will proceed with the inclusion through the paper inclusion form. It will be send by fax to the biostatistics unit 04-67-61-31-18 and project manager 04-67-61-47-02.

In the absence of a request for derogation, the biostatistics unit will return by fax the response to the investigator with the inclusion number and the dose level of the patient.

Then the CRA will **immediately fill out the data in the e-CRF** via https://ecrfcval.icm.unicancer.fr/CSOnline/ in order that an automatic reply can be sent by e-mail to confirm the success of the inclusion procedure to the:

- Representative of Sponsor – project manager,
- Investigator,
- Data manager,
- Statistician,
- Pharmacist

Once the patient is registered, he/she is considered to be enrolled in the study.

5. Visit Schedule

5.1 Tabulated overview

Tabulated overview Folfirinox-R - Phase I/II	Screening		Treatment							Evaluation (Every 8 weeks)	End of treatment	Safety Follow-up	Follow-up	End of study
	D-21	D-7	Cycle 1		Cycle 2		Cycle 3		≥Cycle 4					
Cycles			**C1D1**	**C1D8**	**C2D1**	**C2D8**	**C3D1**	**C3D8**	**≥C4**					
Baseline documentation														
Informed consents[1]	X													
Demographics	X													
Complete medical history	X													
Eligibility Criteria checked [2]	X	X												
Physical examination[3]	X	X	X		X		X		X	X	X	X	X	
β-HCG blood test[4]		X												
Laboratory Studies														
12-lead ECG[5]	X		X[8]		X		X		X		X			
Complete blood count		X	X[8]	X	X	X	X	X	X		X			
Coagulation		X	X[8]		X		X		X		X			
Electrolyte panel		X	X[8]		X		X		X		X			
Chemistry panel[6]		X	X[8]	X	X	X	X	X	X		X			
Liver function test[7]		X	X[8]	X	X	X	X	X	X		X			
Tumor markers (ACE and CA 19-9)		X								X	X	X		

Tabulated overview Folfirinox-R - Phase I/II	Screening		Treatment							Evaluation (Every 8 weeks)	End of treatment	Safety Follow-up	Follow-up	End of study
	D-21	D-7	Cycle 1		Cycle 2		Cycle 3		≥Cycle 4					
Cycles			C1D1	C1D8	C2D1	C2D8	C3D1	C3D8	≥C4					
Urinary analysis[9]		X	X		X		X		X		X			
cfDNA analysis for RAS. UGT1A1 and serum uracil for evaluating DPD	X													
Imaging assessments														
Radiologic Tumor assessment[10]	X									X[11]	X[12]	X[13]		
Other Clinical Assessments														
DLT assessment[14]					X		X		X					
ECOG		X	X		X		X		X		X			
Body weight, BSA, height[15]		X	X		X		X		X	X	X			
Blood pressure[16]		X	X		X		X				X	X		
Concomitant medications		X	X		X		X		X		X	X		
Adverse events[17]		X	X		X		X		X		X	X	X[21]	
Drug dispensing			X		X		X		X					
Drug accountability					X		X		X		X			
Post-study survival status												X	X	
Anti-cancer medications												X	X	
Patient's diary checking[18]					X		X		X		X			
Ancillary studies														
EDTA tubes (3 X 7 ml) cfDNA[19]		X								X	X			
Paraffin block for analysis of DDR1[20]														X

[1]Written informed consent will be obtained for pre-screening and for full study
[2]Eligibility criteria will be checked for pre-screening and for full study
[3]Including skin assessment for toxicities
[4]Pre-menopausal women of childbearing potential only
[5]12-lead ECG will be performed before and after the administration of Oxaliplatin during the three first cycles (Phase I and II) beyond cycle 3, ECG will be performed before administration of oxaliplatin
[6]Includes: albumin, creatinine, creatinine clearance calculated according MDRD, lipase, glucose, TSH (every 6 weeks of CXD1), , total protein and uric acid
[7]Liver function tests will be performed weekly during the three first cycles of treatment
[8]Not required at day 1 of cycle 1 if those were completed within 7 days
[9] Dipstick assessment with pH, protein, glucose, bilirubin, ketones, blood cells and leucocytes
[10]CT scan of the abdomen, pelvis and chest or if the patient is allergic to iodine contrast agents, hepatic MRI and CT scan of the pelvis and chest without injection; RECIST criteria version 1.1
[11]CT-Scans will be performed every 8 weeks
[12]If the last radiological tumor assessment > 1 month
[13]CT-Scan of safety follow-up will be performed if only it weren't done at the EOT visit
[14]Period for DLT assessment is the three first cycles (only Phase I)
[15]Height only at screening
[16]Blood pressure will be monitored every other week during the first 3 cycles of treatment
[17]Continuously from screening until FU visit, 30 days after last administration of study drug
[18]A treatment diary will be handed over to patient on cycle 1 day 1
[19]Three EDTA tubes will be collected at baseline, every 8 weeks during treatment and at the end of treatment
[20]Paraffin-embedded human solid tissue blocks will be sent off at room temperature at the end of the enrollments
[21]Only for unstabilized adverse events since the end of treatment

5.2 Screening period

Enrollment into FOLFIRINOX-R will be performed in two stages with two separate informed consent forms. Initially, all potential patients will consent to undergo molecular testing.

Molecular testing :

Only patients with RAS mutated tumor status, wild-type homozygous status of DPD and wild-type homozygous, heterozygous status of UGT1A1will be screened for the study treatment. **Each centre will choose its DPD and UGT1A1 genotyping laboratory. For your information a list is provided by the sponsor (cf appendix 1). The sponsor will bear the cost of the genotyping analysis (we draw your attention to the analysis of phenotyping which will not be reimbursed by the sponsor).**

A second consent form to screen for the clinical study (Clinical Trial Consent).

Both consent processes are independent of each other.

The following procedures and assessments will be performed **around 21 days of starting study Drug :**

- Obtainment of two informed consents
- A blood sample will be collected then will be shipped to laboratory that you will have chosen. To determine the DPD and UGT1A1 status (cf appendix 1). Check with the laboratory for the number, type and volume of blood tubes
- Documentation of RAS mutation
- Eligibility criteria checked
- Physical examination including review of all organ systems, examination of pertinent organ systems).
- Radiological tumor assessment using the RECIST criteria, version 1.1 (see appendix 4) must be performed. (CT scan of the abdomen, pelvis and chest or hepatic MRI and CT scan of the pelvis and chest without injection).
  A PET scan is not acceptable for radiological evaluation
- All additional suspected sites of disease should be imaged. An appropriate radiological evaluation should be obtained if bone metastases are suspected (e.g., bone scan)
- 12-lead ECG
- Complete medical history including demographics, allergies, prior surgery and prior chemo/radiation therapy with documentation of treatment response. See section XX for detailed instructions on the differentiation between medical history and adverse events

The following procedures and assessments will be performed **within 7 days of starting study drug:**

- Eligibility criteria checked
- ECOG performance status (appendix 5)
- Adverse events
- Physical examination including review of all organ systems, examination of pertinent organ systems, weight, BSA and height.
- A CBC with differential should be performed: RBC, hemoglobin, hematocrit, platelet count and WBC. WBC must include differential neutrophil, lymphocyte, monocyte, basophil and eosinophil counts
- Coagulation panel: Prothrombin time (PT) or the International Ratio of PT (PT-INR) and Partial Thromboplastin Time (PTT)
- Electrolyte panel: sodium, potassium, calcium, magnesium, chloride, phosphate, bicarbonate
- Chemistry panel : albumin, lipase, glucose, serum creatinine, clearance calculated according MDRD, uric acid, , protein total, TSH
- Liver function test panel: Aspartate Amino-Transferase (AST), Alanine Amino-Transferase (ALT), bilirubin (total and direct), alkaline phosphatase, GGT, Lactic Dehydrogenase (LDH)
- Three 7-ml EDTA tubes for cfDNA (not supplied). After centrifugation, the plasma will be frozen at -80°c until shipment.
- Tumor markers : CEA (Carcino-Embryogenic Antigen), CA 19.9 (Carbohydrate Antigen 19-9)
- Urine analysis: PH, protein, glucose, bilirubin, ketones, blood cells and leukocytes
- The blood pressure must be monitored every other week for the three first cycles of study treatment.

The blood pressure will be recorded by the patient and entered onto his treatment diary. Blood pressure measurements will be performed in patients sitting for 5 minutes prior to the evaluation.

- A β-HCG dosage for women of childbearing potential. Post-menopausal women with no menses for at least 1 year or surgically sterilized women will not be required to undergo a pregnancy test.

- Record of all concomitant medications except Homeopathy. All medicines and significant non-drug therapies taken within 7 days before study treatment must be recorded in the e-CRF.

5.3 Treatment period

After all screening assessments have been completed and the patient's eligibility has been confirmed and documented, the patient will be enrolled.

The following assessments should be performed on the first day of each cycle (FOLFIRINOX + Regorafenib except C1D1 prior to receiving study treatment (+/- 3 days) :

- DLTs assessment for phase I from C2D1 to C4D1 (three first cycles),

- Physical examination with weight, body surface area (if the patient's body weight changes by more than 10 % then BSA will be recalculated for Regorafenib and it will be recalculated for any change of weight for Irinotecan). The physical examination includes skin assessment for toxicities,

- ECOG performance status,

- Adverse events documentation (including Start/Stop dates, seriousness, CTC notation and grading, relationship to study drug, outcome and action taken) using CTCAE V5.0,

- Concomitant medications (including start/stop dates, dose, indication),

- 12-lead ECG : It will be performed before and after oxaliplatine administration during the three first cycles of Phase I/II,

- The following laboratory evaluations are not required at Day 1 of Cycle 1 if these were completed within 7 days of starting study drug treatment. Otherwise, these laboratory evaluations are required on Day 1 of each cycle:

  - ➔ CBC with differential should be performed: RBC, hemoglobin, hematocrit, platelet count and WBC. WBC must include differential neutrophil, lymphocyte, monocyte, basophil and eosinophil counts,

  - ➔ Coagulation panel: Prothrombin time (PT) or the International Ratio of PT (PT-INR) and Partial Thromboplastin Time (PTT)
    If a patient is on warfarin or phencoumarone with stable PT/INR at baseline, the PT/INR should be assessed on Day 15 of Cycle 2. If either of these values is above the acceptable range, the doses should be modified and the assessments should be repeated every fortnight until it is stable,

  - ➔ Electrolyte panel: sodium, potassium, chloride, magnesium, calcium, bicarbonates, phosphate,

  - ➔ Chemistry panel : albumin, lipase, glucose, serum creatinine, clearance calculated according MDRD, uric acid, , protein total, TSH every 6 weeks,

  - ➔ Hepatic panel: Aspartate Amino-Transferase (AST), Alanine Amino-Transferase (ALT), bilirubin (total and direct), GGT, alkaline phosphatase, Lactic Dehydrogenase (LDH).

- Urine analysis: PH, protein, glucose, bilirubin, ketones, blood cells and leukocytes

- Drug dispensing,

- Drug accountability (pharmacy). To have complete control over the distribution and use of the study drug, the drug accountability must be performed on Day 1 for (Regorafenib) of each cycle.

  A patient's diary is given on C1D1. It will allow to patient to write down his oral intakes and blood pressure values. It will be checked out at each cycle by C2D1.

- The blood pressure must be monitored every other week for the three first cycles of study treatment,

  The blood pressure will be recorded by the patient and entered onto his treatment diary. Blood pressure measurements will be performed in patients sitting for 5 minutes prior to the evaluation.

The following assessments should be performed on day 8 of cycle 1, 2 , 3 :

- A CBC with differential should be performed: RBC, hemoglobin, hematocrit, platelet count and WBC. WBC must include differential neutrophil, lymphocyte, monocyte, basophil and eosinophil counts

- Chemistry panel: albumin, total protein, lipase, glucose, serum creatinine, clearance calculated according MDRD, uric acid

- Liver function test panel: Aspartate Amino-Transferase (AST), Alanine Amino-Transferase (ALT), bilirubin (total and direct), GGT, Lactic Dehydrogenase (LDH)

The following assessments should be performed at each evaluation i.e (every 8 weeks):

- Tumor markers CEA (Carcino-Embryogenic Antigen), CA 19.9 (Carbohydrate Antigen 19-9)

- Radiological tumor assessment using the RECIST criteria, version 1.1 (see appendix 4) must be performed. (CT scan of the abdomen, pelvis and chest or hepatic MRI and CT scan of the pelvis and chest without injection)

- Physical examination with weight, BSA

- Three 7-ml EDTA tubes for cfDNA (not supplied). After centrifugation, the plasma will be frozen at -80°c until shipment.

5.4 End of treatment Visit

The end of treatment corresponds to the last treatment administered.

When a patient is taken off treatment, the following assessments should be performed within 14 days after study treatment has stopped provided the last clinical and laboratory evaluations > 7 days.

- Physical examination with weight, BSA
- ECOG performance status
- Adverse events documentation (including Start/Stop dates, seriousness, CTC notation and grading, relationship to study drug, outcome and action taken) using CTCAE V5.0
- Concomitant medications
- 12-lead ECG
- A CBC with differential should be performed: RBC, hemoglobin, hematocrit, platelet count and WBC. WBC must include differential neutrophil, lymphocyte, monocyte, basophil and eosinophil counts
- Coagulation panel: Prothrombin time (PT) or the International Ratio of PT (PT-INR) and Partial Thromboplastin Time (PTT)
- Electrolyte panel: sodium, potassium, calcium, magnesium and chloride
- Chemistry panel : albumin, lipase, phosphate, glucose, serum creatinine, clearance calculated according MDRD, uric acid, protein total,

- Liver function test panel: Aspartate Amino-Transferase (AST), Alanine Amino-Transferase (ALT), bilirubin (total and direct), GGT, alkaline phosphatase, Lactic Dehydrogenase (LDH)

- Tumor markers: CEA (Carcino-Embryogenic Antigen), CA 19.9 (Carbohydrate Antigen 19-9)

- Three 7-ml EDTA tubes for cfDNA (not supplied). After centrifugation, the plasma will be frozen at -80°c until shipment.

- Urine analysis: PH, protein, glucose, bilirubin, ketones, blood cells and leukocytes

- A radiological tumor assessment using the RECIST criteria, version 1.1 (see appendix 4) must be performed if the last radiological assessment > 1 months. (CT scan of the abdomen, pelvis and chest or hepatic MRI and CT scan of the pelvis and chest without injection)

- The blood pressure will be recorded by the patient and entered onto his treatment diary. Blood pressure measurements will be performed in patients sitting for 5 minutes prior to the evaluation.

- Drug accountability (pharmacy)

- Patient's diary checking

5.5 Follow-up

Safety Follow-Up Visit

Patients have to be evaluated for symptoms and adverse events in a visit **30 days (+/- 7 days)** after permanently stopping study treatment. This contact may be completed via telephone. The following assessments should be performed:

- Vital status
- Anti-cancer medications
- Physical examination

- A radiological tumor assessment using the RECIST criteria, version 1.1 (see appendix 4) must be performed if only it weren't performed at the end of treatment visit.
  (CT scan of the abdomen, pelvis and chest or hepatic MRI and CT scan of the pelvis and chest without injection).

- Tumor markers : CEA (Carcino-Embryogenic Antigen), CA 19.9 (Carbohydrate Antigen 19-9) if not done at the EOT visit
- Concomitant medications (including anti-cancer medication)
- Adverse events documentation
- The blood pressure must be performed if only it weren't performed at the end of treatment visit.

Follow-up every three months for 3 years

- Vital status
- Anti-cancer medications
- Physical examination
- Adverse events documentation (only for unstabilized adverse events since the end of treatment)

5.6 End of study

- Paraffin-embedded human solid tissue blocks will be sent off at room temperature at the end of the enrollments.

6. Treatments

6.1 Experimental treatment or procedures

Patients having signed informed consent form will receive after registration the treatment.
Patients are eligible for repeated treatment cycles in the absence of disease progression and non-manageable adverse events.
The IV investigational products (IP) will be prepared according to the chemotherapy safety standards (appendix 6).

FOLFIRINOX administration (Phase I and II):

FOLFIRINOX will be administered as per standard procedures: every 14 days (**1 cycle = 14 days**):

- Oxaliplatin (Eloxatin® or generic drug): 85mg/m² on day 1, IV infusion over 2 hours, immediately followed by
- Folinic acid 400 mg/m² or Calcium Levofolinate 200mg/m² given as a 2-hour IV infusion, with the addition, after 30 minutes of
- Irinotecan (Campto® or generic drug): 150-180 mg/m² as per dose-level, given as a 90-minute intravenous infusion through a Y-connector immediately followed by
- 5-Fluorouracil: 400mg/m² IV bolus then 2400mg/m² over 46 hours continuous infusion.

Irinotecan infusion has to be preceded by a subcutaneous injection of atropine: 0.25mg to prevent cholinergic syndrome (in absence of contraindication).

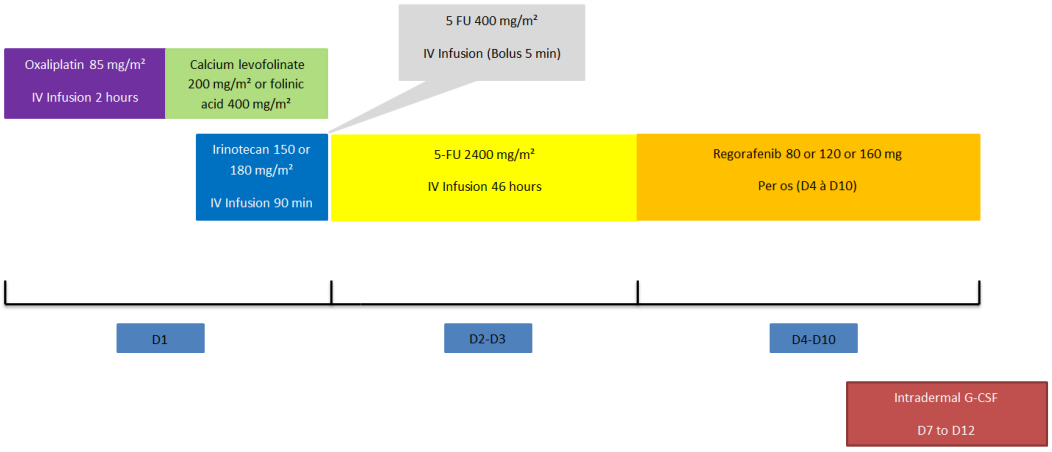
The next cycle starts on day 15. Each cycle will be delivered every 2 weeks.

With this treatment, prophylactic G-CSF will be systematically given after each course from Day 7 to Day 12.

REGORAFENIB administration (Phase I and II):

-On days 4–10 of each cycle, all patients will receive Regorafenib orally once daily depending on dose levels for phase I and RPD2 for phase 2.

- 1 cycle = 15 days



6.2 Drug packaging and labelling

5-FU, Oxaliplatin, Irinotecan

Oxaliplatin, irinotecan, 5-Fluorouacil and calcium levofolinate will be taken in the usual stock.

Regorafenib

For List of excipients and Storage: See Investigator's brochure (appendix 7).

The investigational drug regorafenib must be exclusively used for the investigation specified in this protocol, and it will only be accessible to authorized staff. The sponsor delegate labelling, packaging and shipping of product during the study to Sodia. Sodia will perform this prestation in accordance with applicable Good Manufacturing Practices.

Regorafenib will be provided by Sponsor as film-coated tablets of 40 mg in 30-tablet bottles.

The investigational product(s) label will bear sponsor's name, address and telephone number, the EudraCT number, product name, dosage form and strength, batch number, expiration date, required storage conditions and required caution statements as applicable.

6.3 Shipment, storage conditions and accountability and destruction

The experimental drug regorafenib, provided by the sponsor, will be distributed to the pharmacy at the investigational center by Sodia in accordance with the current Good Distribution Practices guidelines.
The pharmacist of the trial site will receive numbered treatment and will aknowledge receipt of all the shipments by sending to the distributor a form duly completed.
Investigational medicinal products will have to be stored in locked room with limited access and in accordance with the recommendations of the manufacturer.
The pharmacist of the health care site will keep accurate records of the drugs delivered, used, unused or destroyed.
The clinical research assistant mandated by the sponsor will be in charge of verifying the accounting records for the supplied medicinal products and ensure that an accounting form is validated and signed by the pharmacist of the health care center prior to any demand for destruction.
Sites will be provided with an initial supply when activated, and after sites can order supplies as and when they need them. A form will be provided to the site when they are activated.
The pharmacist is responsible for a safe and proper handling and storage of the investigational medicinal products at the investigational center. The investigational products must be stored in a locked facility with restricted access to the pharmacist and authorized personnel, and under environmental conditions consistent with the drug manufacturer recommendations (SmPC for FOLFIRINOX or IB for Regorafenib).

Storage requirements of regorafenib: Regorafenib bottles must be stored in the original carton under refrigeration at a temperature between 2°C and 25° C until the time of use. Bottles will be kept tightly closed.

Storage requirements of irinotecan: Irinotecan must be kept in the outer carton in order to protect from light.
The Irinotecan concentrate for solution for infusion should be diluted and used immediately after opening. However, if dilution takes place in controlled and validated aseptic conditions, the Campto® solution for infusion can be used (infusion time included) within 12 hours when stored at room temperature, or within 24 hours when stored in a refrigerator at 2°C to 8°C after dilution/reconstitution.

Storage requirements of oxaliplatin: after dilution in 5% glucose, chemical and physical in-use stability has been demonstrated for 48 hours at +2°C to +8°C and for 24 hours at +25°C. From a microbiological point of view, this infusion preparation should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C unless dilution has taken place in controlled and validated aseptic conditions.

Storage requirements of 5-Fluorouacil: do not store above 25°C. Keep container in the outer carton to protect from light. Do not refrigerate.
Store the preparation at a temperature between + 15°C and +25°C. After dilution, immediate use is recommended. However, chemical and physical in-use stability has been demonstrated for 8 hours at a temperature between + 15°C and +25°C.

Storage requirements of calcium levofolinate: The lyophilisat must be kept at a temperature <30°C, protected from light and humidity. After preparation, the solution may be kept for 24 hours below 30°C. It may be conserved longer in a refrigerator at a temperature between 2°C and 8°C and in the dark.

All Temperature excursions relating to the shipping or storage of regorafenib (in line with the below table 3) will be reported to ICM as soon as the site becomes aware. In terms of what constitutes a temp excursion for regorafenib, this is summarized below:

Table 3 : Storage Instructions :

Between 2°C - 25°C.

Permitted temperatures: not limited between > 25°C and ≤ + 30°C, 15 days between > + 30°C and ≤ + 40°C, less than 5 days between 40°C and ≤ + 60°C, less than 5 days between > - 18°C and ≤ + 2°C.

Temperature logs should be kept updated by the pharmacist, to document adequate storage during the trial.

The investigator/pharmacist must ensure that the investigational product is administrated only to patients enrolled in this trial. The investigational product must not to be used outside the context of the trial protocol.

The pharmacist or the authorized staff must document the receipt, the dispensation, and the return or destruction of all investigational products received during this trial. Records on investigational products delivery to the center, the inventory at the center, the use by each patient, and the return to the sponsor or destruction by the site must be implemented and maintained by the pharmacist or another appropriately trained individual at the investigational center. Will be reported on these records at least dates, quantities, batch numbers of the investigational products Forms will be provided by the sponsor to ensure trial treatment accountability.

The pharmacist will implement an accounting of medicinal products dispensed, used and unused.

This process will be monitored by the ICM CRA during the trial. The CRA will check that the accountability documentation has been filled in and signed by the pharmacist before the investigational products, used and unused, are destroyed.

The destruction will take place in the investigator centers under the responsibility of their pharmacist in accordance with national regulatory requirements, and with prior formal agreement from the sponsor. A certificate of destruction, identifying concerned products, will be given to the sponsor.

6.4 Treatment duration

12 cycles have to be delivered consecutively or not.

Indeed, treatment can be temporarily stopped to perform surgical resection or regional procedures (radiofrequency, cryoablation, radiation therapy) if the disease become accessible to them but if it happens, before the end of the 12 planned cycles, the treatment

has to be resumed within 4 to 8 weeks after the loco-regional procedure has been completed in order to reach a total number of 12 cycles delivered.
If a surgery or a regional procedure is considered, we recommend respecting a time period of 4 weeks between the last chemotherapy and the procedure.

After 12 cycles, patients whose metastases are not progressing and are still unresectable will receive regorafenib (experimental regimen and at the same dose) until progression or toxicity.

6.5 Expected Toxicities

The expected adverse events of Oxaliplatine, 5 FU and Irinotecan are described in the respective Summaries of Product Characteristics (SmPC). Refer to the latest current version on the public drug database website (appendix 7) for:
- Elvorin
- 5 FU
- OXALIPLATINE
- IRINOTECAN

Refer to the latest investigator's brochure for Regorafenib.

6.6 Dose modification and Dose delay

FOLFIRINOX

Table 4 : Hematological criteria for dose modification/interruption of Folfirinox

CBC on D15	CYCLE DELAY	DOSE REDUCTION		
		Irinotecan (CPT-11)	Oxaliplatin (L-OHP)	LV5FU**
PNN ≥1.5 x 10^9/l and plat. ≥100 x 10^9/l	No cycle delay	no dose reduction		
PNN <1.5 x 10^9/l	Treatment delayed until PNN ≥1.5 x 10^9/l (until D29 if necessary). In case of no recovery on D29, treatment stop, *	1st episode: dose reduction to 120 mg/m² 2nd episode: maintain dose at 120 mg/m² 3rd episode: treatment stop	1st episode: no dose reduction 2nd episode: reduce dose to 60 mg/m² 3rd episode: treatment stop	1st episode: no dose reduction 2nd episode: no dose reduction 3rd episode: treatment stop
Plat. <100 x 10^9/l	Delay treatment until recovery (plat. ≥100 x10^9/l). If no recovery on D29, treatment stop	1st episode: no dose reduction 2nd episode: reduce dose to 120 mg/m² 3rd episode: treatment stop	1st episode: reduce dose to 60 mg/m² 2nd episode: maintain dose at 60 mg/m² 3rd episode: treatment stop	1st episode: no dose reduction 2nd episode: reduce the dose by 25% 3rd episode: treatment stop

Measures in case of hematological toxicity during the inter-cycle interval (nadir):

-Febrile neutropenia* isolated -Grade 4 neutropenia > 7 days -Infection concomitant with grade 3-4 neutropenia	**1st episode**: reduce irinotecan dose to 120 mg/m2 **2nd episode**: in addition reduce oxaliplatin dose to 60 mg/m2 **3rd episode**: discuss further treatment reduction, maintain only LV5FU if necessary.
Grade 3-4 Thrombopenia	**1st episode**: reduce the dose of oxaliplatin to 60 mg/m2 **2nd episode**: in addition reduce the irinotecan dose to 150 mg/m2 and reduce 5-FU IV continuous by 25 %. (If the irinotecan dose of patient is already at 150 mg/m², reduce to 120 mg/m² and reduce 5-FU IV continuous by 25%). **3rd episode**: **stop oxaliplatin and irinotecan, continue LV5FU**

**Definition*: *occurring during a period of medullar hypoplasia (PNN <500/mm3) with fever >38.5°C.*

Table 5 : Dose modifications in case of digestive toxicities

EVENTS	DOSE REDUCTION
-Isolated grade **3-4** diarrhea or -Diarrhea + fever and/or grade 3-4 neutropenia	**1st episode**: reduce irinotecan to 120 mg/m^2 **2nd episode**: reduce oxaliplatin to 60 mg/m^2 and reduce 5-FU continue by 25 % **3rd episode**: **stop irinotécan**
Recurrent diarrhea (>48 h) despite high doses of loperamide	No dose reduction for irinotecan, oxaliplatin and 5-FU after recovery except if grade 3-4 diarrhea, or diarrhea + fever and/or grade 3-4 neutropenia

Table 6 : Dose modifications in case of Peripheral neuropathy:

Toxicity	Duration of toxicity		
	≤7 days	>7 days and <14 days	Persisting between cycles
Paresthesia/dysesthesia without functional alteration (grade 1 NCI)	no modification	no modification	no modification
Paresthesia/dysesthesia with functional alteration not impacting activities of daily living (grade 2 NCI)	no modification	no modification	**60 mg/m^2**
Paresthesia/dysesthesia with pain or functional alteration impacting activities of daily living (grade 3 NCI)	**60 mg/m^2**	**60 mg/m^2**	stop
Persistent paresthesia/dysesthesia, incapacitating	NA	NA	stop
Acute laryngopharyngeal dysesthesia	Prolong infusion duration to 6 hours.		

If oxaliplatin is stopped because of neurotoxicity, irinotecan and 5-FU should be continued.

Table 7 : Dose modifications in case of other specific toxicities:

Toxicity	Recommandations
Cardiac(angina pectoris or myocardial infarction)	Immediately and definitively stop 5FU
Alopecia	Refigerants helmets: - Not recommended with oxaliplatin (paraesthesia) - Not suitable in cases of bone metastases of the cranial vault
Extravasation (including oxaliplatin)	- Stop immediately the infusion - Do not remove the needle or catheter - Aspirate through the same needle maximum infiltrated product - Local ice Application (15-20 minutes every 4-6 hours for 72 hours) - Local Corticosteroid - Check daily the infiltrated site - Surgical Opinion in doubt
Allergy to oxaliplatin	- Stop immediately the infusion of oxaliplatin - Infusion Polaramine / steroids - Filling solution for infusion (macromolecules) if necessary - Do not take the oxaliplatin infusion same day - Restart treatment with oxaliplatin for the next cure with: o Infusion of polaramine before oxaliplatin o Infusion of oxaliplatin during 6 h

Recommendations in case of QT/QTc prolongation > 500msec:
Oxaliplatin will be stopped. Patients will be referred to a cardiologist and monitored in a hospital with continuous cardiac activity recording performed until resolution to grade 1 or baseline.

Recommendations in case of mucositis or hand-foot syndrome:
These toxicities are caused by 5-FU. If grade 3-4 toxicity occurs, continuous 5-FU IV infusion will be reduced by 25% for the remaining cycles.

Dose adaptation in case of bilirubin elevation:

If bilirubin increase is > 1.5 ULN, it is preferable to postpone chemotherapy, because irinotecan is eliminated via biliary pathway, and check the presence of a tumoral relapse or obstruction of bile duct. Indication of chemotherapy will be retained if these two diagnoses are eliminated. However, it will be preferable to stop irinotecan if bilirubin elevation is persistent.

Recommendations in case of Other toxicities:

Other toxicities with > grade 2, except anemia and alopecia, may justify a dose reduction of 25%. If it is medically indicated, for instance, reduction of irinotecan to 120 mg/m2 and/or oxaliplatin to 60 mg/m2 and/or 5-FU decreased by 25 % in function of the type of toxicity.

REGORAFENIB

Table 8 : Dose modification/interruption for non-hematological adverse events related to regorafenib (except hand-foot skin reaction, hypertension, and liver function test abnormalities)

Severity grade	Dose interruption	Dose reduction	Dose for subsequent cycles
Grade 0-2	No interruption of therapy	No change	No change
Grade 3	Interrupt therapy until toxicity resolves to Grade ≤ 2	Decrease dose by 40 mg (one tablet)	If toxicity remains ≤ Grade 2, dose re-escalation may be considered at the discretion of the investigator. If dose is re-escalated and toxicity (≥ Grade 3) recurs, institute permanent dose reduction
Grade 4	Interrupt therapy until toxicity resolves to Grade ≤ 2	Decrease dose by 40 mg (one tablet). Permanent discontinuation may be considered at the investigator's discretion.	–

[a] Excludes alopecia, non-refractory nausea/vomiting, non-refractory hypersensitivity, and non-clinically significant and asymptomatic laboratory abnormalities

Table 9 : Hematological criteria for dose modification/interruption of regorafenib

Grade[a]	ANC (10^9/L)	Platelets (10^9/L)	Dose interruption	Dose modification
0-2	>1.0	≥50	No interruption of therapy	No change
3	<1.0 – 0.5	<50 – 25	Interrupt therapy until toxicity resolves to Grade ≤ 2[b]	1st and 2nd occurence: no change 3rd occurrence : Decrease dose by 40 mg (one tablet)
4	<0.5	<25	Interrupt therapy until toxicity resolves to Grade ≤ 2[b]	1st and 2nd occurence: no change 3rd occurrence : Decrease dose by 80 mg (two tablets)

[a] Applies to all hematological toxicities; absolute neutrophil count (ANC) and platelet count displayed as examples.

[b] If no recovery after 28 day interruption, treatment will be discontinued

[c] Dose will not be re-escalated to original dose level after reduction for toxicity. If more than 2 dose reduction steps are required, treatment will be discontinued

Dose modifications required for study drug-related increases in ALT and/or AST levels and requirements for monitoring are provided in Table 10. During the first 3 cycles of treatment, ALT, AST, and bilirubin must be obtained at baseline and monitored weekly, even if values are normal.

Table 10 : Dose modifications in case of drug-related liver function test abnormalities

Observed elevations of ALT and/or AST	Occurrence	Recommended measures and dose modification
≤5 times upper limit of normal (ULN) (maximum Grade 2)	Any occurrence	Continue regorafenib treatment. Monitor liver function weekly until transaminases return to < 3 times ULN (Grade 1) or baseline.
> 5 times ULN ≤ 20 times ULN (Grade 3)	1st occurrence	Interrupt regorafenib treatment. Monitor transaminases weekly until return to < 3 times ULN or baseline. Restart: If the potential benefit outweighs the risk of hepatotoxicity, re-start regorafenib treatment, reduce dose by 40 mg (one tablet), and monitor liver function weekly for at least 4 weeks.
	Re-occurrence	Discontinue treatment with regorafenib permanently.
>20 times ULN (Grade 4)	Any occurrence	Discontinue treatment with regorafenib permanently.
>3 times ULN (Grade 2 or higher) with concurrent bilirubin >2 times ULN	Any occurrence	Discontinue treatment with regorafenib permanently. Monitor liver function weekly until resolution or return to baseline. Exception: patients with Gilbert's syndrome who develop elevated transaminases should be managed as per the above outlined recommendations for the respective observed elevation of ALT and/or AST.

Dose modifications and measures in case of hand-foot skin reaction (HFSR)/palmar-plantar erythrodysesthesia syndrome are provided in Table 11.

Table 11 : Dose modifications and measures for HFSR

Skin toxicity grade	Occurrence	Recommended dose modification and measures
Grade 1	Any	Maintain dose level and immediately institute supportive measures for symptomatic relief.
Grade 2	1st occurrence	Decrease dose by 40 mg (one tablet) and institute supportive measures. If no improvement occurs despite dose reduction, interrupt therapy for a minimum of 7 days, until toxicity resolves to Grade 0-1. A dose re-escalation is permitted at the discretion of the investigator.
	No improvement within 7 days or 2nd occurrence	Interrupt therapy until toxicity resolves to Grade 0-1. When re-starting treatment, decrease dose by 40 mg (one tablet). A dose re-escalation is permitted at the discretion of the investigator.
	3rd occurrence	Interrupt therapy until toxicity resolves to Grade 0-1. When re-starting treatment, decrease dose by 40 mg (one tablet). A dose re-escalation is permitted at the discretion of the investigator.
	4th occurrence	Discontinue treatment with regorafenib permanently.
Grade 3	1st occurrence	Institute supportive measures immediately. Interrupt therapy for a minimum of 7 days until toxicity resolves to Grade 0-1. When re-starting treatment, decrease dose by 40 mg (one tablet). A dose re-escalation is permitted at the discretion of the investigator.
	2nd occurrence	Institute supportive measures immediately. Interrupt therapy for a minimum of 7 days until toxicity resolves to Grade 0-1. When re-starting treatment, decrease dose by 40 mg (one tablet).
	3rd occurrence	Discontinue treatment with regorafenib permanently.

Suggestions:

Control of calluses
Before initiating treatment with regorafenib:

- Check condition of hands and feet
- Suggest a manicure/pedicure, when indicated

- Recommend pumice stone use for callus or ‘rough spot’ removal.

During regorafenib treatment:

- Avoid pressure points
- Avoid items that rub, pinch or create friction

Use of creams

Apply non-urea based creams liberally, e.g.,

- Cetaphil
- Aveeno
- Norwegian Formula
- Eucerin

Keratolytic Creams: Use sparingly and only to affected (hyperkeratotic) areas

- Urea-based creams
- Salicylic acid 6%

Alpha Hydroxy Acids (AHA) based creams

- Approximately 5-8% provide gentle chemical exfoliation
- Apply liberally two times each day

Topical analgesics like lidocaine 2% to be considered for pain control

Topical corticosteroids should be considered for subjects with Grade 2 or 3 hand-foot skin reaction. Avoid systemic steroids.

Cushions

Protect tender areas

- Use socks/gloves to cover moisturizing creams
- Wear well-padded footwear
- Use insole cushions or inserts (e.g., silicon, gel)

- Foot soaks with tepid water and Epsom salts

Table 12 : Dose modification/interruption and management of treatment-emergent hypertension

Severity grade	Definition	Antihypertensive therapy	Dose modification/interruption
Grade 1	Prehypertension: SBP 120-139 mmHg or DBP 80-89 mmHg	None	Continue study drug. Consider increased BP monitoring
Grade 2	SBP 140-159 mmHg or DBP 90-99 mmHg or symptomatic increase in DBP >20 mmHg or to >140/90 mmHg if previously within normal limits	Treat with the aim to achieve DBP ≤ 90 mmHg. If S/DBP previously within normal limits, start antihypertensive monotherapy. If subject is taking antihypertensive medication, titrate the dosage up.	Continue study drug. If symptomatic, delay dose until symptoms resolve AND diastolic BP ≤ 90 mmHg Restart dose at same dose level.
Grade 3	SBP ≥ 160 mmHg or DBP ≥ 100 mmHg or ≥1 antihypertensive drug or more intensive antihypertensive therapy required than previously	Treat to DBP ≤ 90 mmHg. Start antihypertensive medication. and/or Increase dose of current antihypertensive medication. and/or add additional antihypertensive medication(s)	Delay dose until DBP ≤ 90 mmHg and, if symptomatic, until symptoms resolve. A restart dose will be at the same dose level. If BP not controlled with more intensive therapy, reduce dose to Dose reduction step -1 If Grade 3 hypertension recurs after dose reduction and antihypertensive therapy, reduce dose to Dose reduction step -2
Grade 4	Life-threatening consequences (malignant hypertension): transient or permanent neurologic deficit, hypertensive crisis	--	Discontinue therapy

In cases only one value is >Grade 1 (e.g., 155/88 mmHg), the guidelines provided for the highest grade should be followed. Patients requiring interruption of study treatment > 4 consecutive weeks must discontinue study drug.
If BP remains controlled for ≥ one full cycle, dose re-escalation is permitted at the investigator's discretion

Blood pressure will be recorded by the treating physician and entered onto the e-CRF.

Any blood pressure that is out of normal range must be reported to the treating physician.
Blood pressure measurements considered out of normal range are diastolic ≥100 mmHg and systolic ≥ 150 mmHg, or a ≥ 20 mmHg increase in diastolic measurement if the measurement was previously within normal limits.

The dose modification schedule for treatment emergent hypertension during regorafenib dosing should be followed (see [Table 12]). Patients' blood pressure (BP) measurements will be monitored and appropriate treatment to effectively control hypertension under regorafenib treatment is strongly recommended.
The selection of anti-hypertensive medication used in this setting should be performed at the investigator's discretion, considering possible site-specific treatment guidelines. All medication should be recorded in the subjects e-CRF.

Termination of regorafenib :

In the event of gastrointestinal perforation or fistula develops
In the event of reversible Posterior Encephalopathy Syndrome (REPS)
-In the event of the appearance of cardiac ischemia and/or infarction, severe bleeding, severe hypertensive crisis

6.7 Authorized associate procedures and treatment

All medication which is considered necessary for the patient's welfare, and which is not expected to interfere with the evaluation of the study drug, may be given at the discretion of the Principal Investigator. All concomitant medications (including start/stop dates, dose frequency, route of administration and indication) must be recorded in the patient's source documentation, as well as in the appropriate pages of the e-CRF.

6.7.1 Other treatments/procedures

Authorized concomitant medications:

- Atropine
- Anti-emetics
- Alpha hydroxyl acids, keratolytic, non urea creams
- Topical corticoids

- Antihistaminics
- Contrast agent
- Treatment with non-conventional therapies (for example homeopathy, vitamins or acupuncture), and vitamin/mineral supplements is acceptable provided that they do not interfere with the study endpoints, in the opinion of the Investigator.
- It is advised not to use the association of warfarine (Coumadine®) with chemotherapy. It is preferable to use heparin and therapeutic anticoagulation with low-molecular weight heparin. If warfarine cannot be avoided, the rate of prothrombin must be checked more frequently and INR monitored every fortnight until INR/PTT is stable.
- Bisphosphonates
- G-CSF and other hematopoietic growth factors may be used during the study in the management of acute toxicity such as febrile neutropenia when clinically indicated or at the discretion of the investigator.
- Patients taking chronic erythropoietin are authorized.

6.8 Prohibited treatment

-Other antitumor treatments (chemotherapy, hormonotherapy, immunotherapy, biological response modifier, targeted therapy) or approved therapies during this trial or within 30 days are prohibited.

-St-John's wort

-Herbal medicine and grapefruit juice

-Yellow fever vaccine.

-live attenuated vaccines

-Pimozide (Orap®) and cisapride (Prepulsid®) are strictly contraindicated: they are associated with a major risk of disorder of the ventricular rhythm (notably twisting spuces).

-Immunosuppressive agents (eg ciclosporin, tacrolimus): Excessive immunosuppression with risk of lymphoproliferation.

-Bone marrow transplant or stem cell rescue.

-Radiotherapy within 28 days prior to first dose of treatment.

6.9 Main medications that can interact with regorafenib

Inhibitors of CYP3A4 and UGT1A1/UGT1A9/inducers of CYP3A4

In vitro data indicate that regorafenib is metabolized by cytochrome CYP3A4 and uridine diphosphate glucuronosyl transferase UGT1A9.

Administration of ketoconazole (400 mg for 18 days), a strong CYP3A4 inhibitor, with a single dose of regorafenib (160 mg on day 5) resulted in an increase in mean exposure (AUC) of regorafenib of approximately 33%, and a decrease in mean exposure of the active metabolites, M-2 (N-oxide) and M-5 (N-oxide and N-desmethyl), of approximately 90%. It is recommended to avoid concomitant use of strong inhibitors of CYP3A4 activity (e.g. clarithromycin, grapefruit juice, itraconazole, ketoconazole, posaconazole, telithromycin and voriconazole) as their influence on the steady-state exposure of regorafenib and its metabolites has not been studied.

Co-administration of a strong UGT1A9 inhibitor (e.g. mefenamic acid, diflunisal, and niflumic acid) during regorafenib treatment should be avoided, as their influence on the steady-state exposure of regorafenib and its metabolites has not been studied.

Administration of rifampicin (600 mg for 9 days), a strong CYP3A4 inducer, with a single dose of regorafenib (160 mg on day 7) resulted in a reduction in AUC of regorafenib of approximately 50%, a 3- to 4-fold increase in mean exposure of the active metabolite M-5, and no change in exposure of active metabolite M-2. Other strong CYP3A4 inducers (e.g. phenytoin, carbamazepine, phenobarbital and St. John's wort) may also increase metabolism of regorafenib. Strong inducers of CYP3A4 should be avoided, or selection of an alternate concomitant medicinal product, with no or minimal potential to induce CYP3A4 should be considered.

UGT1A1 and UGT1A9 substrates

In vitro data indicate that regorafenib as well as its active metabolite M-2 inhibit glucuronidation mediated by UGT1A9 whereas M-5 only inhibits UGT1A1 at concentrations

which are achieved *in vivo* at steady state. This indicates that co-administration of regorafenib may increase systemic exposure to UGT1A1 and UGT1A9 substrates.

Breast cancer resistance protein (BCRP) and P-glycoprotein substrates

Administration of regorafenib (160 mg for 14 days) prior to administration of a single dose of rosuvastatin (5 mg), a BCRP substrate, resulted in a 3.8-fold increase in mean exposure (AUC) of rosuvastatin and a 4.6-fold increase in C_{max}.

This indicates that co-administration of regorafenib may increase the plasma concentrations of other concomitant BCRP substrates (e.g. methotrexate, fluvastatin, atorvastatin).

Inhibitors of P-glycoprotein and BCRP/Inducers of P-glycoprotein and BCRP

In vitro studies indicate that the active metabolites M-2 and M-5 are substrates for P-glycoprotein and BCRP. Inhibitors and inducers of BCRP and P-glycoprotein may interfere with the exposure of M-2 and M-5. The clinical significance of these findings is unknown.

CYP isoform-selective substrates

In vitro data indicate that regorafenib is a competitive inhibitor of the cytochromes CYP2C8 (Ki value of 0.6 micromolar), CYP2C9 (Ki value of 4.7 micromolar), CYP2B6 (Ki value of 5.2 micromolar) at concentrations which are achieved in vivo at steady state (peak plasma concentration of 8.1 micromolar). The in vitro inhibitory potency towards CYP3A4 (Ki value of 11.1 micromolar) and CYP2C19 (Ki value of 16.4 micromolar) was less pronounced.

A clinical probe substrate study was performed to evaluate the effect of 14 days of dosing with 160 mg regorafenib on the pharmacokinetics of probe substrates of CYP2C8 (rosiglitazone) CYP2C9 (S-warfarin), CYP 2C19 (omeprazole) and CYP3A4 (midazolam).

Pharmacokinetic data indicate that regorafenib may be given concomitantly with substrates of CYP2C8, CYP2C9, CYP3A4, and CYP2C19 without a clinically meaningful drug interaction.

Antibiotics

The concentration-time profile indicates that regorafenib and its metabolites may undergo enterohepatic circulation (see section 5.2). Co-administration with neomycin, a poorly absorbed antimicrobial agent used for eradicating the gastrointestinal microflora (which may interfere with the enterohepatic circulation of regorafenib) had no effect on the regorafenib exposure, but there was an approximately 80% decrease in the exposure of the active metabolites M-2 and M-5 which showed *in vitro* and *in vivo* comparable pharmacological activity as regorafenib. The clinical significance of this neomycin interaction is unknown, but

may result in a decreased efficacy of regorafenib. Pharmacokinetic interactions of other antibiotics have not been studied.

Bile salt-sequestering agents

Regorafenib, M-2 and M-5 are likely to undergo enterohepatic circulation. Bile salt-sequestering agents such as cholestyramine and cholestagel may interact with regorafenib by forming insoluble complexes which may impact absorption (or reabsorption), thus resulting in potentially decreased exposure. The clinical significance of these potential interactions is unknown, but may result in a decreased efficacy of regorafenib.

6.10 Main medications that can interact with irinotecan

-Concomitant treatments based on St-John's wort (alternative medecine) are absolutely contraindicated with irinotecan (Campto® or generic drug); this plant decreases the serum concentration of SN-38, the active metabolite of irinotecan.

-The interaction between irinotecan and neuromuscular blocking agents cannot be established. Because of the anticholinesterase activity of IRINOTECAN, drugs with anticholinesterase activity may prolong the neuromuscular blocking effects of suxamethonium and neuromuscular blockade of non-depolarizing agents may be antagonized.

-Several studies have shown that concomitant administration of cytochrome CYP450 3A4-inducing anti-convulsants (such as carbamazepine, phenobarbital or phenytoin) decreased exposure to irinotecan, SN-38 and SN38 glucuronide and reduced their pharmacodynamic effects. The effects of these anti-convulsants result in a 50% or greater decrease in areas under the curve (AUC) of SN-38 and SN-38 glucuronide. In addition to induction of cytochrome CYP450 3A4 enzymes, increased glucuronidation and biliary excretion may play a role in reducing exposure to irinotecan and its metabolites.

-One study showed that co-administration of irinotecan with ketoconazole compared to irinotecan alone resulted in an 87% decrease in AUC of APC and a 109% increase in AUC of SN-38.

-Special attention is required in patients receiving drugs known to simultaneously inhibit (such as ketoconazole) or induce (such as rifampin, carbamazepine, phenobarbital, or

phenytoin) cytochrome CYP450 3A4 metabolism. Concomitant administration of irinotecan with an inducer or inhibitor of this metabolic pathway may alter irinotecan metabolism and should be avoided.

6.11 Main medications that can interact with 5 FU

Metronidazole (Flagyl®) and ornidazole: the concomitant administration of metronidazole can enhance toxicity of 5-FU by decreasing its clearance.
- Allopurinol (Zyloric®): concomitant administration of this product must be avoided (loss of 5-FU efficacy).
-Phenytoin : Risk of convulsions due to decreased digestive absorption of phenytoin alone by the cytostatic, or risk of increased toxicity or loss of cytotoxic efficacy due to increased hepatic metabolism by phenytoin or fosphenytoin.
-Antivitamin K : Significant increase in the effect of antivitamin K and hemorrhagic risk. If association cannot be avoided, more frequent monitoring of INR. Dosage adjustment of antivitamin K during cytotoxic treatment and 8 days after discontinuation.
-Interferon alpha : Increased gastrointestinal toxicity of 5-FU.
-Drugs that may affect dihydropyrimidine dehydrogenase (DPD) activity :
A clinically significant interaction between the antiviral Sorivudine and fluorouracil prodrugs has been observed, resulting from the inhibition of dihydropyrimidine dehydrogenase, the enzyme responsible for the catabolism of fluorouracil and its prodrugs, by Sorivudine or chemically related analogues. Precautions should be taken when using fluorouracil in combination with drugs that may affect the activity of dihydropyrimidine dehydrogenase.
-Cimetidine may increase the blood concentration of fluorouracil.
In the majority of cases, cytostatics are given in combination, which leads to an increase in efficacy, but at the cost of a possible increase in toxicity.
-Yellow fever vaccine is absolutely contraindiqued
Risk of fatal generalized vaccine disease.
-Live attenuated vaccines (except antiamarile) is not recommended
Risk of life-threatening, widespread vaccine-preventable disease. This risk is increased in subjects already immunocompromised by the underlying disease. Use inactivated vaccine when available (polio).

6.12 Main medications that can interact with Oxaliplatin

The drugs that prolong QTc and/or cause twisting spikes have to be used with caution (see appendix 8).

7. Blinded independent central review (BICR)

A central review of CT-scans is planned for patients found progression-free at 48 weeks**.** They will be submitted to a independent panel of radiologists for review of tumor response.

7.1. Shipment procedure and storage

Compact Discs (CDs) will be anonymized and sent by postmail or transferred to PACS server of ICM if it's possible technically.

It is important to the integrity of the study that all imaging studies are forwarded to the independent panel of radiologist in a timely manner throughout the study (by the end of treatment of patient).

8. Ancillary Studies

8.1. Activity of DDR1 as a predictor of efficacy of regorafenib

Paraffin-embedded human solid tissue blocks will be sent off at room temperature at the end of the inclusions and addressed to:

Mrs Catherine VIGLIANTI
collection manager
Institut régional du cancer de Montpellier
Centre de ressources biologiques
208, rue des Apothicaires – Parc Euromedecine
34298 Montpellier CEDEX 5
Tel : +33 (0) 4.67.61.25.31 – Fax : +33 (0) 4.67.63.28.73
catherine.viglianti@icm.unicancer.fr

Paraffin-embedded human solid tissue blocks will be returned to the home institution upon completion of ancillary study.

Actually, with this translational research, we aim to assess DDR1 activity as a predictor of efficacy in mCRC patients treated with a regorafenib-based therapy.

The research will be led by Serge Roche, Centre de Recherche en Biologie cellulaire de Montpellier

Methodology: *DDR1 activity in CRC samples*: DDR1 activity will be measured from tumor protein-lysates with the pathscan phospho-DDR1 (panTyr) ELISA kit (CST Company).
Inhibition of DDR1 metastatic activity by regorafenib: DDR1 kinase overexpression in HCT116 and SW620 CRC cells increases their invasive capacities in Boyden chambers and their capacity to form colosphere when cultured in suspension in the presence of collagen (17). We will test the capacity of regorafenib (1-500nM) to block these DDR1 transforming properties *in vitro*. DDR1 kinase overexpression in Luc+ SW620 cells increases their metastatic abilities when spleen-injected in nude mice (17). We will test the capacity of regorafenib (50mg/kg/d) to block this DDR1 metastatic function. Drug treatment will be started when metastatic nodules are already developed in recipient animals (i.e. at day 7). Metastatic development will be analyzed by measuring over time luciferase activity in live animals (imaging of the whole animal) and a metastatic index will be deduced from livers of sacrified animals.

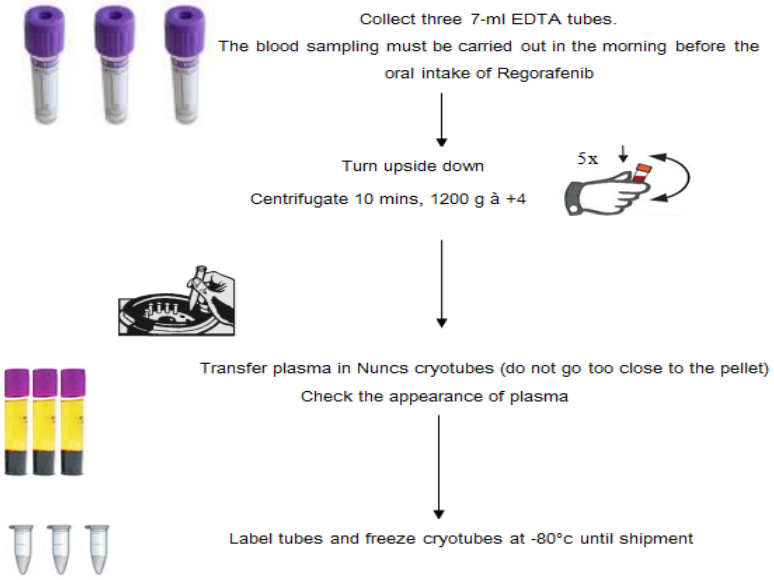
8.2. cfDNA monitoring

8.2.1. Sample timeline

Three EDTA tubes will be collected at baseline, every 8 weeks during treatment and at the end of treatment (not supplied).

8.2.2. Processing of samples

Three 7-ml EDTA tubes will be taken at various times and centrifuged within 4 hours at 1200g for 10 minutes at 4°c. After centrifugation, the plasma will be frozen at -80°c until shipment.



8.2.3. Shipment and analysis

Mrs Catherine VIGLIANTI
Blood collection manager
Institut régional du cancer de Montpellier
Centre de ressources biologiques
208, rue des Apothicaires – Parc Euromedecine
34298 Montpellier CEDEX 5
Tel : +33 (0) 4.67.61.25.31 – Fax : +33 (0) 4.67.63.28.73
catherine.viglianti@icm.unicancer.fr

The second centrifugation at 16 000 g for 10 minutes at 4°c and analysis will be carried out by :

Dr Alain Thierry
Equipe de recherche intégrée en Cancérologie de Montpellier (INSERM)
Institut de Recherche du Cancer de Montpellier (IRCM)
208, rue des Apothicaires – Parc Euromédecine
34298 Montpellier CEDEX 5
Tél : +33 (0) 4.67.61.24.42 ; +33 (0) 6.63.82.19.94
Fax : +33 (0) 4.67.61.24.53
Alain.thierry@inserm.fr

cfDNA will be extracted using either the QIAmp DNA blood Mini kit (Qiagen, CA) or the Maxwell automatic extractor according to the standardized guidelines which were defined for pre-analytical conditions (unpublished data).

CfDNA total concentrations and fragmentation level will be determined by either by targeted or sequencing methods.

A banking sample is planned at ICM-CRB, Montpellier.

9. Subject withdrawal/end of study

9.1. DISCONTINUATION OF TREATMENT

Discontinuation of treatment does not represent withdrawal from the trial. As certain data on clinical events beyond treatment discontinuation are important to the study, they must be collected through the subject's last scheduled follow-up, even if the subject has discontinued treatment. Therefore, all subjects who discontinue trial treatment prior to completion of the treatment regimen will still continue to participate in the trial.

Patient may be discontinued from study treatment at any time if the patient, the Investigator, or the Sponsor feels that it is not in the patient's best interest to continue on study. The following is a list of possible reasons for early discontinuation of study treatment:

- Disease progression (unless there is reasonable evidence of clinical benefit to justify continuation on treatment – to be discussed with the Sponsor)
- In the investigator's opinion, continuation in the study treatment would be detrimental to the patient's well-being
- Protocol violation requiring discontinuation of study treatment
- Patient is not compliant with study procedures
- Patients with a β-HCG test consistent with pregnancy. Pregnancy will be notified to the sponsor.
- Any adverse event that cannot be adequately managed with dose modifications, including dose interruption > 28 days (unless there is reasonable evidence of clinical benefit to justify continuation on the protocol – to be discussed with the Sponsor)
- Discontinuation of treatment during more than 4 weeks
- Patient death
- New cancer
- Lost to follow-up

  (The Investigators should make every effort to recontact the patient to identify the reason why he/she failed to attend the visit, and to determine the patient health status, including at least the vital status. Attempts to contact such patients must be documented in the patient's records (e.g., times and dates of attempted telephone contact, receipt for sending a registered letter).

9.2. WITHDRAWAL FROM THE TRIAL

A subject must be withdrawn from the trial if the subject or subject's legally acceptable representative withdraws consent from the trial.

If a subject withdraws from the trial, they will no longer receive treatment or be followed at scheduled protocol visits.

9.3. END OF STUDY

The end of the trial corresponds to the last follow-up of the last patient.

9.4. ASSESSMENT CRITERIA

Phase I: Identify the maximum-tolerated dose (MTD) of Folfirinox combination with regorafenib in Patients with metastatic colorectal cancer.

Phase II:

Non-progression rate (OR+SD): The tumor response will be assessed by the investigator using RECIST guidelines v1.1 (2009). The non-progression rate will be presented as a percentage with a 95% confidence interval.

Objective response (OR): The tumor response will be assessed by the investigator using RECIST v1.1 criteria, from the first course of chemotherapy, until disease progression. Patients with suggestive symptoms of disease progression should be evaluated at the time of onset of symptoms. An objective response is defined as a complete (CR) or a partial (PR) response.

The best objective response rate will be reviewed at the end of treatment and presented as a percentage with a confidence interval of 95%.

Survival:

Progression-free survival (PFS): Survival Delays will be calculated in months from the date of inclusion to the date of the considered event: First documented disease progression or death from any cause.

Living patients without disease progression will be censored at the last known date.

Rates and median PFS will be estimated using Kaplan-Meier method and presented with its 95% confidence interval.

Overall survival (OS): The overall survival time will be calculated in months from the date of inclusion to the date of death from any cause. Living patients will be censored at the last known date.

Rates and median overall survival will be estimated using the Kaplan-Meier product limit method and presented with its 95% confidence interval.

The median follow-up will be calculated using the "reverse Kaplan-Meier method".

10. Statistical considerations

10.1. SAMPLE SIZE

Phase I

A standard 3 + 3 design will be followed in the dose escalation. A maximum of 24 patients will be enrolled in phase I.

Phase II

With a one-stage Fleming design, α = 5%, β = 20%, p0 (the probability of inefficiency maximum) = 35% and p1 (the probability of minimum efficiency) = 50%, it would be necessary to include 65 evaluable patients (69 patients/ 5% non-evaluable patients).

The association can be considered sufficiently effective (reject null hypothesis) if there are at least 29 success (48 weeks disease control rate) out of 65 evaluable patients, the success rate is significantly greater than 35%.

The association can be considered insufficiently effective (reject alternative hypothesis) if there are 28 or less success out of 65 evaluable patients, the success rate is significantly lower than 50%.

In total, a maximum of 87 (=18 patients for phase I + 69 patients for phase II including 6 patients treated at the RP2D during the phase I) patients will be included.

10.2. STUDY POPULATIONS

Different population of patients may be defined for the analysis:

- Intent To Treat (ITT) population: all included patients.
- Per-Protocol (PP) population: all eligible patients (patients with no major violations of the inclusion/exclusion criteria) and evaluable patients (included treated patients with evaluation at 48 weeks or without evaluation at 48 weeks if progressive or dead patient).
- Safety population: all treated patients who received at least one dose of treatment.

10.3. STATISTICAL METHODS

A statistical analysis plan (PAS) will be written before the closed database. All statistical analyses will be performed on ITT population, on PP population for efficacy analysis and on Safety population for safety analysis. Populations are defined in section 10.2.

Descriptive analyses will be performed using median and range for continuous parameters, frequency and percentage for categorical variables.

Incidence rate of DLT and Incidence rates of adverse events and serious adverse events will be carried using frequencies and percentages at each dose level for phase 1.

The primary phase II endpoints 48 weeks disease control rates, will be described using percentage and its associated 95% confidence interval.

The median follow-up will be calculated using the reverse Kaplan-Meier method with its confidence interval of 95%.

All event free survival (PFS, OS) will be estimated using the Kaplan-Meier method, and then described using medians and rates with their associated 95% confidence interval.

Statistical analyses will be performed with STATA software (Stata Corporation, College Station, TX, USA).

11. Vigilance and safety control

11.1. ADVERSE EVENTS

11.1.1. DEFINITION

An Adverse Event (AE) is defined as “Any untoward medical occurrence in a patient or clinical investigation subject administered an investigational product and which does not necessarily have a causal relationship with this treatment”. An AE can therefore be any unfavorable and unintended sign (for example: an abnormal laboratory finding), symptom, disease, or worsening of a pre-existing medical condition temporally associated with the use of an investigational product, whether or not considered related to the investigational product.

Only abnormal laboratory findings which are clinically significant should be considered an AE. Abnormal laboratory findings are clinically significant if an active medical intervention is indicated, such as a dose modification of the investigational product ; an interruption of the investigational product; the withdrawal of the investigational product; the introduction of a (symptomatic) treatment; the performance of additional diagnostic procedures; the increase in monitoring frequency.
An AE related to the investigational product is also called an adverse reaction.

11.1.2. COLLECTION AND REPORTING

Every AE occurring during the clinical trial should be recorded on the corresponding page of the Case Report Form. Every AE should be documented, monitored and followed until the AE is recovered or until the safety follow-up visit is performed at 30 days after the withdrawal of the investigational product.

Clinically significant abnormal laboratory findings should be monitored regularly by specific analysis until their values return within the normal reference ranges, to the baseline value or until an adequate explication of the out of range value has been found. Per the applicable regulations, AEs are collected from the moment of signature of the informed consent form until up to 30 days after the withdrawal of the investigational product.

For every AE, the following parameters will be documented by the investigator:

- A clear description of the event using the adequate medical terms;
- The seriousness of the event;
- The severity or grade of the event (severity criteria are described in the next paragraph);
- The onset and end dates of the event;
- The actions taken and the necessity to introduce a corrective treatment or not;
- Whether the AE caused or not the withdrawal of the subject from the study;
- The outcome of the event. In case of a non-fatal outcome, the AE should be documented until recovered, until the return to baseline conditions of the event or until stabilization of the event's sequelae (the nature of the sequelae should be documented) ;
- The causality between the event and the investigational product *;*

- The eventual causality between the event and the study procedures (time laps without treatment, complementary assessments required by the protocol, etc.…), the study indication, a concomitant treatment, a concomitant pathology or another factor.

11.1.3. SEVERITY CRITERIA

The severity criteria should not be mistaken with the seriousness criteria which determine the conditions of notification. The severity or grade of adverse events is evaluated by the investigator following the NCI-CTCAE classification version 5.0 (appendix 9).

The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

- **Grade 1** = Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2** = Moderate; minimal, local or non-invasive 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 AE.

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

11.2. SERIOUS ADVERSE EVENTS AND NEW EVENT

11.2.1. DEFINITION

A **Serious Adverse Event (SAE)** is an adverse event which:

- results in death
- is life-threatening
- requires in-patient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability or incapacity

- Is a congenital anomaly or birth defect
- Is medically relevant

Life-threatening in this context refers to an event in which the patient was at risk of death at the time of the event; it does not refer to a reaction that hypothetically might have caused death if more severe.

A hospitalization scheduled by the protocol (biopsy, chemotherapy...) is not considered a SAE. A hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE is not considered a SAE. A hospitalization planned prior to patient enrollment is not considered a SAE, provided that his occurrence/outcome is clearly not aggravated by the investigational product.

The terms “disability” and “incapacity” match with all physical/psychological temporary or permanent handicaps, clinically significant with consequences for the physical or mental functioning and/or the quality of life of the patient.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious events, such as important medical events that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Such events are considered serious with seriousness criterion “medically relevant”. Examples of such events are allergic bronchospasm, torsade de pointes (appendix 8) or convulsions.

Other examples of serious adverse events with seriousness criterion “medically relevant” are second primary malignancies and any suspected transmission via a medicinal product of an infectious agent.

For every SAE the investigator and the sponsor evaluate separately the possible causal relationship to the investigational product. These evaluations might be different one from the other (for example: in the investigator’s opinion the SAE is not related to the investigational product and in the sponsor’s opinion the SAE is related to the investigational product).

A **New event** (article R1123-46 du CSP) is:

Any new data that may lead to a re-assessment of the benefit/risk ratio of the clinical trial or the investigational medicinal product (IMP), to modifications of the use of the IMP or the conduct of the trial or modifications of documents regarding the trial or to the suspension or termination of the clinical trial or to modify the protocol of the trial concerned or other similar trials.

For a first in man study conducted in healthy volunteers: any serious adverse reaction (SAR) of the IMP is considered to be a new event

11.2.2. **URGENT SAFETY MEASURE (USM)** (ARTICLES L.1123-10 ET R. 1123-62 CSP)

When a suspicion of an Unexpected Serious Adverse Reaction (SUSAR) or a New Event is likely to affect the safety of the subjects, or the IMP is likely to affect the safety of the participant who lend themselves to it with immediate endangerment, the sponsor and investigator put in place Urgent Safety Measure (USM) to protect the subjects against this immediate hazard, the sponsor and the investigator concerned take the necessary appropriate Urgent Safety Measures (USM).

11.2.3. SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION

A SAE is qualified as a Suspected Unexpected Serious Adverse Reaction (SUSAR) when a causal relationship between the investigational product and the SAE is suspected and when the nature, the severity, the frequency or the evolution of the reaction does not match with the information available in the reference document. The sponsor evaluates the unexpectedness of the SAE by consulting the SmPC of Oxaliplatin, 5 FU, Irinotecan and the investigator's brochure in force for Regorafenib.

11.2.4. PREGNANCY

For female patients treated with the investigational product, the treatment with this product should be discontinued immediately at the occurrence or suspicion of occurrence of pregnancy and the patient should be withdrawn from the study (after confirmation of the pregnancy by a urine or blood test).

The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

In accordance with the recommendations for fertility preservation, the investigator may propose to the patient a protocol of conservation of ovocytes for women and of sperm cells for men.

11.2.5. SAE, NEW EVENT, URGENT SAFETY MEASURE, PREGNANCY NOTIFICATION PROCEDURE

11.2.5.1. SAE NOTIFICATION PROCEDURE

Every SAE, expected or unexpected, occurring during the study period (from the moment of signature of the informed consent form until up to 30 days after the withdrawal of the investigational product) should be notified to the sponsor without any delay using the "Serious Adverse Event Notification Form" (appendix 10). This form should be completed following the completion instructions (appendix 10) and sent by email to the Clinical Research Pharmacovigilance Unit of ICM.

Clinical Research Vigilance Unit

ICM – Institut régional de Cancérologie de Montpellier
208, rue des Apothicaires, 34298 Montpellier
Tel: +33 4 67 61 45 68 – Fax: +33 4 67 61 31 04
E-Mail: Notification-EIG-DRCI@icm.unicancer.fr

Every SAE occurring beyond the 30 days period after the withdrawal of the investigational product, judged by the investigator to be related to the investigational product, should also be notified to the sponsor in the same conditions as every other SAE.

The "Serious Adverse Event Notification Form" should be completed in English and only one diagnosis or one symptom (except for linked symptoms) should be reported to enable MedDRA coding. If several symptoms are documented in the source documents, only the main symptom will be reported as verbatim on the notification form.

After the initial notification, a follow-up report should be completed and faxed every time complementary information on the SAE becomes available. Finally, when the case is closed, a final report with the complete information should be completed and sent by email to the Clinical Research PharmacoVigilance Unit :

E-Mail: Notification-EIG-DRCI@icm.unicancer.fr

Complementary information or clarification could be requested by the sponsor using Data Clarification Forms (DCFs). The sponsor could also ask the site to send the anonymized medical records or laboratory findings corresponding to the SAE. In case of a SUSAR a narrative of the case in English is to be provided by the investigator.

11.2.5.2. NEW EVENT / URGENT SAFETY MEASURE (USM)/ NOTIFICATION PROCEDURE

Any New Event and/or Urgent Safety Measure occurring during the study period should be notified to the sponsor without any delay, to Clinical Research Pharmacovigilance Unit:

E-Mail: Pharmacovigilance-icm105@icm.unicancer.fr

Clinical Research Vigilance Unit
ICM – Institut régional de Cancérologie de Montpellier
208, rue des Apothicaires, 34298 Montpellier
Phone: +33 4 67 61 45 68

11.2.5.3. PREGNANCY NOTIFICATION PROCEDURE

Pregnancies and suspected pregnancies occurring during the study period from the signature of the informed consent form until up to 4 months after withdrawal of investigational medicinal products for female patients and 6 months after withdrawal of investigational medicinal products for female partners of male patients, are immediately reportable events.
Every pregnancy or suspicion of pregnancy should be notified to the Sponsor without any further delay.
Pregnancy notification will be done using the "pregnancy notification form" (appendix 11). This form should be completed using the filling instruction guide (appendix 11) and sent by email to the pharmacovigilance unit (see above).
The Investigator should inform the Sponsor of the pregnancy follow-up by using the same “Pregnancy Notification Form” (appendix 11) as for the initial notification. If the outcome of the pregnancy falls within the scope of the definition of serious adverse event (spontaneous

abortion requiring hospitalization, fetal death, congenital abnormality…) the investigator should follow the Serious Adverse Event notification.
If it is a paternal exposure, the investigator must obtain the agreement of the pregnant women to collect the information on pregnancy.

11.2.5.4. SUMMARY CHART OF NOTIFICATION BY TYPE OF EVENT

Type of Event	**Notification requirements.**	**Notification period to the sponsor**
Adverse Event	Case Report Form	No Immediately reportable events
Serious Adverse Event	SAE Notification Form (initial+ Follow up, if necessary) + Case Report Form	Immediately reportable events without any delay to the sponsor
New Event	Written report	Immediately reportable events without any delay to the sponsor
Urgent Safety Measure (USM)	Written report	Immediately reportable events without any delay to the sponsor
Pregnancy	Pregnancy notification form	From confirmation of pregnancy

11.2.6. OBLIGATION OF THE SPONSOR

The ICM, as the sponsor of the trial, receives all SAE Notification Forms and evaluates the imputability and the expectedness of the SAEs. In case of a “New event” or any urgent safety measures, the sponsor shall inform immediately ANSM and the concerned CPP of the new events and the measures taken.
The declaration of eventual SUSARs and “New event” or any urgent safety measures (USM) to the competent authorities is delegated to UNICANCER, 101 rue de Tolbiac 75013 Paris (Tel: +33 1 44 23 04 04). UNICANCER submits the SUSARs within the required regulatory timelines to the European Medicine Agency (EMA) via EudraVigilance and the competent national authorities (ANSM).

The risk-benefit balance of the study is evaluated continuously by the Clinical Research Vigilance Unit of ICM and this risk-benefit balance will be discussed in the periodic safety reports. These reports will contain all required regulatory aspects and will be submitted to the competent authority (ANSM) and CPP within the regulatory timeframe.

SUMMARY CHART OF NOTIFICATION BY TYPE OF EVENT
ART. R1123-53

Type of Event	Initial notification period to the Competent Authority (ANSM, CPP)	Follow up notification period to the Competent Authority (ANSM, CPP)
SUSARs (Death, or life threatening)	Immediately reportable events With any delay after the sponsor has taken notice of this event	Within maximum 7 days after the sponsor has taken notice of this event
Other SUSARs	Within 15 days after the sponsor has taken notice of this event	Within maximum 8 days after the sponsor has taken notice of this event
New Safety Event	Immediately reportable events With any delay after the sponsor has taken notice of this event	Within maximum 8 days after the sponsor has taken notice
Urgent Safety Measures (USM)	Immediate implementation of MUS Immediate information (without any delay)	Request for substantial modification Within maximum 15 days after the sponsor has taken notice

11.2.7. INDEPENDENT SAFETY COMMITTEE (ISC)

An Independent Safety Committee (appendix 12) is organized as an Independent Data Monitoring Committee, comprising independent experts in clinical research and/or the study indication.

The ISC will be constituted of 3 persons: two oncologists and a methodologist not participating in the trial.

The first scheduled time point will be at the end of phase I. According to the number of DLTs and after the advice of the IDMC, the sponsor will decide to continue on to phase II or stop the trial. The sponsor could ask to organise an additional independent safety committee in the event of SUSARs during Phase I.

During a trial the ISC could be requested to review:

- Real-time and cumulative safety data for evidence of study-related adverse events;
- Adherence to the protocol;
- Factors that might affect the study outcome or compromise the trial data (such as protocol violations, losses to follow-up, etc.);

- Data relevant to proceeding to the next stage of the study, if applicable.

The safety data will be provided to the ISC members by the Biostatistics Unit, and / or the Clinical Research Pharmacovigilance Unit and / or the Study Coordinator.

12. Quality assurance and control

12.1. Data collection

Database management

The Database will be hosted by the Institut du Cancer Montpellier (ICM) – Val d'Aurelle, Unité de Biométrie – CTD INCa, 208 rue des Apothicaires – Parc Euromédecine – 34298 Montpellier cedex 5 – France under the responsibility of Sophie Gourgou.
Database management will be provided by an electronic Case Report Form (eCRF) developed using the CSOnline module of Ennov Clinical® software.
In case of a technical problem on the eCRF, the investigator may refer to the specific operating procedure of the eCRF or contact directly:

ICM – Unité de Biométrie – CTD INCa
From Monday to Friday 9am-5pm
Email: support.ecrf@icm.unicancer.fr
Fax: +33 (0)4 67 61 37 18 Tél. : +33 (0)4 67 61 45 48 / 24 52

Secure access password

Each user will receive in his/her personal mailbox an access code (login) and a personal password automatically generated from CSOnline to connect to the eCRF via the following website: https://ecrfcval.icm.unicancer.fr/CSOnline/.

A password non-disclosure certificate is signed by the principal investigator engaging his/her responsibility regarding the confidentiality of the access codes for all users of the eCRF in his/her center.

Data collection

The study data will be recorded directly by the identified and declared persons of each center, via the eCRF, and will be controlled and validated according to specific procedures.
At the end of the study and once all the eCRF data are validated, the investigator will log in and sign all the pages in order to validate the data entered for each patient.
The sponsor will create and send an electronic copy (PDF file) to the investigator. This copy must be printed and signed by the investigator, to be archived at the investigator's site.

12.2 Trial monitoring

To ensure the authenticity and credibility of all data, in accordance with the "Décision portant sur les Bonnes Pratiques Cliniques, 24 November 2006", the sponsor establishes a system of quality assurance consisting in:

- The management and monitoring of the trial according to the sponsor's (ICM) procedures;
- The data quality control of the investigational centers by the monitor which involves:
  - verifying that the protocol, as well as the current ICH-GCP guidelines and the national regulatory requirements are accurately followed,
  - verifying the informed consent and the eligibility of each patient
  - verifying that the e-CRF data is consistent and in concordance with the source documents,
  - verifying the notification of each SAE,
  - verifying the drug traceability (dispatching, storage and accountability),
  - verifying (if applicable) that patients are not already participating in another research trial which may exclude their inclusion in the present protocol. The monitor will also verify that patients have not participated in another trial following with, if applicable, an exclusion period before they can participate in another protocol,
- The audit of the participating investigational centers when deemed necessary;

The monitors and CRAs in charge of the trial monitoring will be mandated by the sponsor. They must have access to all the patients' data as necessary for their duty, in accordance with the national regulatory requirements. The monitors and CRAs are bound by professional secrecy under the national regulatory requirements. Written reports must be issued to ensure monitoring visit traceability.

In order to ensure the optimal research quality control, the investigator commits to provide the monitor with direct access to all the patients' files.

12.3 Audits and inspection

As part of its audit program, the sponsor may need to audit some investigational centers. The center and the investigator agree that audits can be carried out by the sponsor or any person duly authorized for at least fifteen years after the trial.

More generally, the investigator center and the investigator undertake to devote the time necessary to audit procedures, control and additional information requested by the sponsor or by a Concerned Competent Authority.

A Competent Authority may also wish to conduct an inspection (during the trial or after its completion). If a Competent Authority requests an inspection, the investigator must inform the sponsor immediately that this request has been made. The investigator must provide a direct access to all source documents.

13. Administrative, ethical and regulatory aspects

13.1. Conduct of the study and responsibilities

The Sponsor

The sponsor undertakes according to the law in force to:

- Take out civil liability insurance,
- Request the approval as well as for any substantial modifications to ANSM (agence nationale de sécurité du médicament et des produits de santé),
- Request the favorable opinion as well as for any substantial modifications to the Committee for the Protection of Persons (CPP),
- Declare to the CPP and the ANSM the beginning and the end of the study,
- Write the final report of the study,
- Inform the competent authority, the CPP and the participants of the research of the results of the study,

- Archive the essential documents of the study in the trial master file for a minimum of 15 years after the end of the research.

The Investigator

It is the responsibility of each investigator to:

- Provide the sponsor with his curriculum vitae,
- Conduct the clinical trial according to the protocol approved by the ANSM,
- Collect written informed consent from each patient entering the trial. One copy is given to the patient, the original is to be kept by the investigator, the last copy will be kept by the sponsor,
- Regularly complete the e-CRF for each patient included in the trial,
- Make available to the CRA mandated by the sponsor the source documents of the patients in order to confront the data with those entered in the e-CRF and to allow their validation,
- Archive all study documents (informed consents) for a period of 15 years,
- Respect the confidentiality of the documents provided to him.

13.2. Subject information and consent

The written informed consent of the patient must be obtained by the investigator or a person designated by the investigator before collecting any personal data. The consent must be signed and dated by the patient and the investigator or the person designated by the investigator to conduct the informed consent interview.

Obtaining informed consent requires the subject to be provided with sufficient information by the investigator. Information for the patients, prepared in accordance with the ICH recommendations, will be made available by the sponsor for the purposes of informed consent collection.

The signature of the consent will be confirmed in the e-CRF by the investigator. The signed and dated statement of this informed consent will be archived in the investigator site file (ISF) so that forms can be retrieved at any time for surveillance, audit and inspection. A signed and dated copy of the subject information and consent form must be given to the subject as soon as it is signed.

The subject information will be revised at each update of important new information that may influence the subject's consent.

13.3. Regulatory authorizations

The research will be carried out in accordance with the French regulations in force, in particular the provisions relating to biomedical research of the Public Health Code, articles L1121-1 and following, the laws of Bioethics, the data protection law, the declaration of 'Helsinki (appendix 13), the Jardé law n ° 2012-300 of March 5, 2012 relating to the research involving the human person (application by the decree 2016-1537 and 1538) and Good Clinical Practices.

Pursuant to the provisions of articles 39 and 40 of the Law (Computing and Liberties) of August 6, 2004 and that of April 27, 2016, patients have a right of access and rectification on the data concerning them and the European Regulation 2016/679 on the protection of individuals with regard to the processing of personal data and on the free movement of such data known as the "GRDP" (General Regulation on Data Protection). They also have a duty to oppose the transmission of these data. These rights are exercised with their investigator who will inform the coordinating center of research as soon as possible.

13.4. Authorization of the biological resource center

The CRB involved in the research has received authorization to preserve and prepare tissues and cells from the human body for transfer for scientific use, Permit No. AC-2014-2196.

13.5. Processing of research data

In accordance with the Decree No. 2016-1872 of December 26th, 2016 published in the Official Journal on December 28th, 2016, the ICM follows the reference methodology MR001 of the National Commission for Data Processing and Freedoms.

13.6. Amendments of the protocol

The sponsor alone is authorized modifying the protocol, in consultation with the trial coordinator.

In accordance with the Articles L.1123-9 and R.1123-35 of the French Public Health Code, any change occurring after the beginning of the research, having an impact on any aspect of

the research, especially on protection of persons, including with regard to their safety, on the conditions for the validity of research, if any, on the quality and safety of experimental drugs, on the interpretation of scientific documents which support the development of research or the modalities of conduct of this one.

A substantial modification request is sent by the sponsor to the ANSM for approval and/or CPP for favorable opinion. Upon receipt of the approval and favorable opinion, the amended version of the protocol is then forwarded to all investigators by the sponsor.

A non-substantial change to the protocol is a minor change or unrestricted clarification of the conduct of the test. These modifications will not be submitted to the competent authorities but will be subject to an agreement between the sponsor and the investigator and will be clearly documented in the follow-up file of the study and will be forwarded to the ANSM and/ or CPP for information.

13.7. Sponsor discontinuation criteria

Premature termination of this study may occur because of a regulatory authority decision, change in approval of ANSM or opinion of the CPP, drug safety problems, or at the discretion of the Sponsor.
If the study is prematurely terminated or discontinued, the Sponsor will promptly notify the Investigator. After notification, the Investigator must notify the respective CPP, and contact all participating patients and the hospital pharmacy (if applicable) within a 4-week time period. As directed by the Sponsor, all study materials must be collected and all eCRFs completed to the greatest extent possible.

14. Financing and Insurance

14.1. Financing of Research

We have a partnership contract with Bayer HealthCare that will finance this study.

14.2. Insurance

Insurance has been subscribed by the sponsor (ICM) to SHAM (Contract No. 140.474) for all subjects included in the study as of their inclusion (that is, from the date of signing of the consent enlightened) in accordance with the provisions of Decree 2006-477 of 26 April 2006,

in order to cover the obligations placed on them under Article L 1121-10 of the French Public Health Code.

15. Publication policy and communication

15.1. PUBLICATION POLICY

The coordinator will attempt to submit a publication within one year from the presentation of the final results by biostatistician. No publication or presentation of the results of this trial may be made without the agreement of the sponsor and the coordinator.
The authors of the publication are as follows:
- the main writer (in principle the coordinator unless specifically requested by the latter);
- a limited number of investigators limited to 1 per center according to the order of recruitment. A weighting may be envisaged for large recruiting centers;
An investigator who has not included will be thanked at the end of the article;
-the biostatistician will be in 3rd author ranking and may be 1st or 2nd author according to the publications derived;
-a representative of the DRCI will be included in the authors (scientific writer, director of the DRCI or project manager depending on their involvement);
-the last author is usually the coordinator of the study (if not the principal author) or someone who has taken decisive action in the design and/or conduct of the study;

If the maximum number of authors authorized by journals is very limited, a restriction will be made by the coordinator with the assistance of the DRCI as the sponsor's representative.
In the case of a derived publication, the authors may be different and reflect the specialty concerned by the article, but the latter must always include at least the name of the coordinator or a clinician of the ICM.
Similarly, when submitting abstracts, the order of authors may vary according to the conference at which the paper is presented.
Acknowledgements:
It may appear in the acknowledgements at the end of the article:
-patients and their families;
-the project manager (s) of the DRCI;
-the data manager (s) and the investigating CRA(s);
-all participants and representatives of the DRCI not included in the authors;

-partners and funders in accordance with the partnership agreements signed with the ICM promoter;

The CRB - ICM should be mentioned either in the "Materials and Methods" section or in the acknowledgements with N°BB-033-00059.

15.2. DATA SHARING STATEMENTS

Will individual participant data be available? Yes

What data in particular will be shared? All of the individual participant data collected during the trial, after deidentification.

What other documents will be available? Study protocol, statistical analysis plan, clinical study report, analytic code.

When will data be available (start and end dates)? Immediately following publication. No end date.

With whom? Anyone wishes to access the data.

For what type of analyses? Any purpose.

By what mechanism will data be made available? The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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17. Appendices