PROTOCOL SUMMARY

SYNOPSIS

A) TRIAL IDENTIFICATION	
SPONSOR – PROTOCOL CODE NUMBER: UC-GIG-1910	
VERSION (NUMBER & DATE): version 3.0 dated 10 February 2022	
TRIAL TITLE: A randomized, phase II study comparing the sequences of regorafenib and trifluridine/tipiracil, after failure of standard therapies in patients with metastatic colorectal cancer. **PHASE (FOR TRIALS ON MEDICINAL PRODUCTS):** II	
ABBREVIATED TITLE: SOREGATT	
INTERNATIONAL COORDINATING INVESTIGATOR: Prof. Michel Ducreux	
NUMBER OF CENTERS: 50 centers	**NUMBER OF PATIENTS:** 340 randomized patients

B) SPONSOR IDENTIFICATION	
NAME:	**UNICANCER** 101, rue de Tolbiac, 75654 Paris Cedex 13 (France)
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C) TRIAL GENERAL INFORMATION
INDICATION: The study population will consist of male and female patients aged ≥ 18 years old with metastatic colorectal cancer after failure of fluoropyrimidine-, irinotecan-, and oxaliplatin-based chemotherapies, as well as EGFR and VEGF inhibitors in patients eligible for these treatments.
TRIAL DESCRIPTION/DESIGN: Multicenter, international, comparative, randomized, open-label, phase II study conducted in two parallel groups.
PRIMARY OBJECTIVE: The primary objective will be to compare the feasibility of the treatment sequences, regorafenib then trifluridine/tipiracil (Arm A) and trifluridine/tipiracil then regorafenib (Arm B). The feasibility will be assessed in terms of percentage of patients able to receive both line of treatment.

SECONDARY OBJECTIVES: The secondary objectives include the comparison between arms of:

- The Overall Survival (OS).
- The Progression-Free Survival in the first treatment line (PFS1).
- The Progression-Free Survival in the second treatment line (PFS2).
- The Disease control rate (DCR).
- The Objective response rate (ORR).
- The Time-to-treatment failure in the first treatment line (TTF1).
- The Time-to-treatment failure in the second treatment line (TTF2)
- The quality of life using patient reported outcomes: QLQ-C30 version 3.0
- The time to deterioration of ECOG PS ≥2
- The tolerance of the treatment sequences (by computing the incidence of adverse events using CTCAE v5.0).

INCLUSION CRITERIA:

The patient must meet all of the following inclusion criteria to be eligible for the study:

1. Patients must have provided informed consent before performing any study specific procedures.
2. Histological or cytological documented adenocarcinoma of the colon or rectum.
3. Patients with metastatic colorectal cancer (stage IV).
4. Measurable disease, defined as at least one unidimensional measurable lesion on a computed tomography (CT) scan according to RECIST v1.1.
5. The patient must have progressed following exposure of all the following agents: one fluoropyrimidine-based chemotherapy (capecitabine or fluorouracil [5-FU]), combined with oxaliplatin and/or irinotecan (including FOLFOX, FOLFIRI or FOLFOXIRI) as well as EGFR and/or VEGF inhibitors in patients eligible for these treatments.
6. Patients considered eligible for treatment with both regorafenib and trifluridine-tipiracil.
7. Male or female patients aged ≥18 years.
8. ECOG performance status of ≤1.
9. Adequate bone marrow, liver and renal functions as assessed by the following laboratory requirements:
   • Total bilirubin ≤1.5 x upper limit of normal (ULN).

• Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 x ULN (≤5 x ULN for patients with liver metastasis).

• Alkaline phosphatase limit ≤2.5 x ULN (≤5 x ULN for patients with liver metastasis).

• Serum creatinine ≤1.5 x ULN.

• International normalized ratio (INR) and partial thromboplastin time (PTT) ≤1.5 x ULN. Patients receiving anticoagulants, such as warfarin or heparin are eligible if there is no prior evidence of an underlying abnormality with coagulation.

• Platelet count ≥75000 /mm3, hemoglobin (Hb) ≥9 g/dL, absolute neutrophil count (ANC) ≥1500/mm3. Blood transfusions to meet this inclusion criterion are not allowed.

10. Women of childbearing potential and men must agree to use a highly effective contraception (<1% failure rate) from the signing of the informed consent form until at least 6 months after the last study drug administration. Women using hormonal contraceptive must also use a barrier method.
11. Women of childbearing potential must have a negative pregnancy test within 7 days before starting study treatment.
12. Patients affiliated to the social security system
13. Patient willing and able to comply with the protocol for the duration of the study including treatment, scheduled visits, and examinations throughout the study, including follow up.

NON-INCLUSION CRITERIA:

Patients who meet any of the following criteria at the time of screening will not be eligible for the study:

1. Patients with symptomatic brain or meningeal metastasis, unless definitive therapy occurred more than 6 months ago and with a confirmation of tumoral control within 4 weeks of starting study treatment.
2. 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 in situ cervical cancer, non-melanoma skin cancer, and superficial bladder tumors: staged Ta (non-invasive tumor), Tis (carcinoma in situ), and T1 (tumor with lamina propria invasion).
3. Prior treatment with regorafenib or any other tyrosine kinase inhibitor.
4. Prior treatment with trifluridine/tipiracil.
5. Known hypersensitivity to any of the study drugs, study drug classes, or study drug excipients.
6. Unresolved toxicity grade >1 (by CTCAE v5.0) caused by prior therapy/procedure, excluding alopecia, hypothyroidism, and oxaliplatin-induced neurotoxicity grade ≤2.
7. Patient with moderate or severe hepatic impairment (Child-Pugh C).
8. Known UGT1A1polymorphisms. History of Gilbert's syndrome.
9. Major surgical procedure, open biopsy, or significant traumatic injury within 28 days before starting study treatment.
10. Chemotherapy within 21 days of starting study treatment.

11. Radiotherapy within 4 weeks of starting study treatment, except for palliative radiotherapy within 2 weeks.
12. Active cardiac disease including any of the following:
    - Congestive heart failure: New York Heart Association (NYHA) class ≥2.
    - Unstable angina (angina symptoms at rest), or a new-onset angina (within the 3 months before enrolment).
    - Myocardial infarction that occurred less than 6 months before enrolment.
    - Cardiac arrhythmias requiring anti-arrhythmic therapy (treatment with beta blockers or digoxin are permitted)
    - Uncontrolled hypertension despite optimal medical management.
13. Arterial or venous thrombotic or embolic events such as cerebrovascular accident (including transient ischemic attacks) within 6 months of starting study treatment. Deep vein thrombosis or active pulmonary embolism that are significant or not adequately controlled on anticoagulation regimen as per investigator's judgement.
14. Ongoing infection grade >2 (CTCAE v5.0).
15. Known history of human immunodeficiency virus (HIV) infection.
16. Active hepatitis B or C, or chronic hepatitis B or C requiring treatment with antiviral therapy.
17. Patients with seizure disorder requiring medication.
18. Patients with a history of any bleeding diathesis, irrespective of the severity.
19. Any hemorrhage or bleeding event grade ≥3 (CTCAE v5.0) within the 4 weeks before starting study treatment.
20. Presence of a wound, ulcer, or bone fracture that is not healing.
21. Patients unable to swallow oral medications.
22. Bowel malabsorption or extended bowel resection that could affect the absorption of regorafenib, occlusive syndrome,
23. Presence of gastro-intestinal fistula or perforation
24. Any illness or medical conditions that are unstable or could jeopardize the safety of the patient and their compliance in the study.
25. Patients participating in another therapeutic study within the 30 days before enrolment.
26. Pregnant or breast feeding women.
27. Person deprived of their liberty or under protective custody or guardianship.

PRIMARY ENDPOINT:

The primary endpoint is the feasibility of the treatment sequence defined as the percentage of subjects who receive at least two cycles of both regorafenib and trifluridine/tipiracil in each arm. Subjects will be

considered as a success if they are administered at least two cycles of each line of therapy, i.e. percentage of patients being treated until the first tumor evaluation.

SECONDARY ENDPOINTS:

- Overall Survival (OS) is defined as the time interval from randomization until death from any cause.
- Progression-free survival 1 (PFS1) is defined as the time interval from randomization until death or the disease progression observed in the first sequence of treatment in each arm, evaluated using RECIST v1.1.
- Progression-free survival 2 (PFS2) is defined as the time interval from randomization until death or the disease progression is observed in the later sequence of treatment in each arm, evaluated using RECIST v1.1.
- Disease control rate (DCR) is defined as percentage of patients with a best response that is not progressive disease (PD) (either complete response [CR], partial response [PR], or stable disease [SD]) during treatment. DCR will be assessed in each study arm
- Objective response rate (ORR) is defined as percentage of patients with a best response being either complete response [CR] or partial response [PR] during treatment. ORR will be assessed in each study arm.
- Time-to-treatment failure 1 (TTF1) is defined as the time from randomization to treatment discontinuation for any reason (including disease progression, treatment toxicity, patient preference, or death) during the first sequence of treatment in each arm.
- Time-to-treatment failure 2 (TTF2) is defined as the time from randomization to treatment discontinuation for any reason (including disease progression, treatment toxicity, patient preference, or death) during the second sequence of treatment in each arm.
- Quality of life data using the patient reported outcomes, QLQ-C30 version 3.0 will be collected during the study.
- The time to ECOG PS ≥2 deterioration is defined as the time interval between randomization and the first documented ECOG PS ≥2 during the study.
- Data concerning adverse events graded using the CTCAE v5.0 will be collected during the study.

These endpoints will be compared between the study arms.

D) INVESTIGATIONAL MEDICINAL PRODUCTS

PRODUCT NAMES AND ADMINISTRATION:

Drug name (INN)	Registered name(1)	Pharmaceutical form	Administration route	Posology
Regorafenib		40 mg film-coated tablets	Per os	160 mg per day during 3 weeks followed by 1 week off of each 4-week cycle except for cycle 1. During first cycle: dose is started at 80mg per day at week 1, 120mg per day at week 2, 160mg per day at week 3, followed by 1 week off.

Drug name (INN)	Registered name(1)	Pharmaceutical form	Administration route	Posology
Trifluridine/ tipiracil		- 15 mg/6.14 mg mg film-coated tablets - 20 mg/8.19 mg film-coated tablets	Per os	35 mg/m^2 Dose administered orally twice daily on Days 1 to 5 and Days 8 to 12 of each 4-week cycle.

THERAPEUTIC REGIMENS:

Patients will be randomized according to a 1:1 ratio to treatment arms A and B.

- Arm A: regorafenib until disease progression or unacceptable toxicity occurs, followed by trifluridine/tipiracil until disease progression or unacceptable toxicity occurs.
- Arm B: trifluridine/tipiracil until disease progression or unacceptable toxicity occurs, followed by regorafenib until disease progression or unacceptable toxicity occurs.

Prior to randomization, they will be stratified according to:

- Country
- ECOG (0 or 1)
- Age (<65 years old or ≥65 years old)

The time span between the end of the first treatment phase and the initiation of second treatment phase should not exceed 4 weeks.

The posology of regorafenib will be as follows: 80mg per day on C1W1, 120mg per day on C1W2, 160mg per day on C1W3, 1 week off (this 4-week period is considered a treatment cycle), followed by regorafenib 160 mg starting from cycle 2.
If a dose is missed, then it should be taken on the same day as soon as the patient remembers. The subject should not take two doses on the same day to make up for a missed dose. In case of vomiting after regorafenib administration, the subject should not take additional tablets.

The starting dose of trifluridine/tipiracil is 35 mg/ m^2 /dose administered orally twice daily on Days 1 to 5 and Days 8 to 12 of each 28-day cycle. The dosage is calculated according to body surface area. The dosage must not exceed 80 mg/dose

If doses are missed or held, the subject must not make up for missed doses.

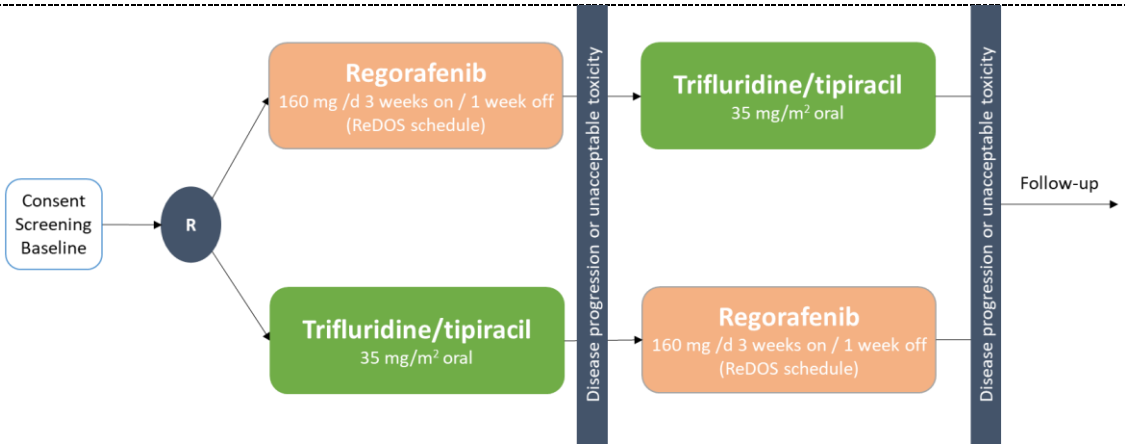
Posology adjustments

Regorafenib
The regorafenib dose may be delayed or reduced in case of clinically significant hematological and other toxicities that are considered at least possibly related to regorafenib. Toxicities will be graded using the NCI-CTCAE v5.0. Regorafenib dose will be modified in increments of 40 mg. The lowest recommended daily dose of regorafenib is 80 mg and the maximum is 160 mg. Thus, if a patient experiences more than two dose reductions, regorafenib should be permanently discontinued.
If a patient experiences several toxicities with conflicting recommendations, the recommendation with the lowest dose of regorafenib to be taken must be used. Recommendations are described in the protocol and in the SmPC. You should always refer to the most recent version of the SmPC for regorafenib (Stivarga®).

Trifluridine/tipiracil
A maximum of 3 dose reductions are permitted to a minimum dose of 20 mg/m^2 twice daily. Dose escalation is not permitted after it has been reduced.
In the event of haematological and/or non-haematological toxicities patients should follow the dose interruption, resumption and reduction criteria stated in the SmPC. You should always refer to the most recent version of the SmPC for trifluridine/tipiracil (Lonsurf®).

Treatment will be discontinued in case of any delay in treatment administration of more than 4 weeks.

TRIAL FLOWCHART:



TREATMENT DURATION:

Study treatment will be continued until disease progression or until unacceptable toxicity occurs. The washout period between the 2 study drugs period should not exceed 4 weeks.

DOSE ESCALATION : No dose escalation possible

E) STATISTICAL ANALYSIS PLAN

REQUIRED NUMBER OF PATIENTS TO BE SCREENED/INCLUDED:

The primary endpoint is the feasibility of the treatment sequence. The hypothesis for the sample size calculation are based on the data published by Moriwaki et.al showing that 50% of the subjects receiving trifluridine/tipiracil were able to receive further treatment as compared to 65% with regorafenib (Moriwaki, Fukuoka et al. 2018). With a Chi-square test between the two arms, a bilateral type I error rate of 5% and a power of 80%, 170 patients are required in each arm, i.e. 340 patients in total.

STATISTICAL ANALYSIS:

Study population

The following populations will be considered:

- Intent-to-Treat (ITT) population will include all randomized patients according to their randomized arm. This population will be used for the analysis of all efficacy endpoints.
- The safety population will include all the patients who have received at least one dose of either drug regardless of treatment period. This population will be used for the safety analysis.

Statistical analysis plan

Statistical data will be presented in the form of:

- percentages for qualitative variables,
- mean and standard deviation or median and range for quantitative variables.

The baseline characteristics of the trial arms will be described, including demographics and laboratory measurements, using descriptive statistics.

All tests will be bilateral tests with a 5% threshold.

All analyses will be performed by using SAS® version 9.4 or newer.

Primary endpoint analysis

The feasibility of the treatment sequence is defined as the percentage of patients who receive at least two cycles of both treatments in each arm, i.e. percentage of patients being treated until the first tumor evaluation. Thus, patients in Arm A, allocated regorafenib then trifluridine/tipiracil, will be considered a success if they received at least two cycles of regorafenib and two cycles of trifluridine/tipiracil. Similarly, patients in Arm B, allocated trifluridine/tipiracil then regorafenib, will be considered a success if they receive at least two cycles of trifluridine/tipiracil and two cycles of regorafenib.

Whenever the patient did not receive the second treatment (i.e toxicity, death, lost to follow-up…), it will be considered as a failure.

The comparison between the two trial arms will be adjusted for the stratification factors with a logistic regression model according to the intent-to-treat principle.

F) SAMPLES COLLECTED FOR TRANSLATIONAL RESEARCH – FRENCH SITES ONLY

SAMPLE TYPES:

TUMOR

- Collection of previously collected and archived paraffin-embedded **tumor samples** from patients in both arms at baseline visit, in order to identify tumor factors predictive of response using immunochemistry.

BLOOD

- **Whole blood** sample will allow the dosing of constitutional/genomic DNA (gDNA) at baseline visit.
- **Plasma samples** will allow the dosing of circulating tumor DNA (ctDNA) concentrations in order to predict tumoral response. Additional plasma samples will allow the dosing of Stanniocalcin-1 (STC1) in order to establish the correlation between clinico-molecular characteristics of patients and STC1 levels.

  Thus, for all patients in both arms: collection of **blood samples** (per patient) are summarized below:
  - at baseline : 4 tubes: 1 for gDNA (whole blood), 2 for ctDNA (plasma) + 1 for STC1 (plasma)
  - during the treatment phase at each study visit (before drug administration on Cycle X Day 1) : 2 plasma tubes (ctDNA) and at the visit corresponding to the first CT-scan evaluation (8 weeks after Phase 1 - Cycle 1 Day 1) : 1 tube of plasma (STC1)
  - at the change of treatment visit : 2 tubes of plasma (ctDNA)
  - at treatment discontinuation visit: 2 tubes of plasma (ctDNA)
  - at progression : 1st progression occurring during treatment period 1 : 1 tube of plasma (STC1) and 2nd progression occurring during treatment period 2 : 1 tube of plasma (STC1)

G) TRIAL DURATIONS

INCLUSION PERIOD: 2 years

TRIAL TREATMENT PERIOD: until disease progression or unacceptable toxicity (approximately 6 months of treatment for both lines of treatment)

FOLLOW-UP: 5 years after the last study treatment stops

DURATION UNTIL PRIMARY ENDPOINT EVALUATION: 3 years

OVERALL TRIAL DURATION (INCLUDING FOLLOW-UP): 7,5 years

SCHEDULE OF VISITS AND ACTIVITIES (SOA)

VISITS	**Baseline visit(s)**	**Visits during first treatment phase**	**Change of study treatment visit**	**Visits during the second treatment phase**	**Study treatment discontinuation visit**	**Long-term follow-up visits**
Visit timelines	*≤28 days before starting treatment*	*On D1 of each 28-day treatment cycle*	*≤4 weeks delay between first and second treatment phases*	*On D1 of each 28-day treatment cycle*	*30±7 days after second treatment discontinuation*	*Every 3±1 months for 3 years and every 6±1 months for 2 years*
DRUG DISPENSING AND ACCOUNTABILITY		**X**		**X**		
Eligibility criteria	**X**					
Signed informed consent form	**X**					
Randomization	**X**					
PHYSICAL EXAMINATION						
Assessment of all systems, vital signs (pulse and blood pressure), weight, and height[a].	**X[1]**	**X[b]**	**X**	**X[b]**	**X**	**X[c]**
ECOG PS	**X[1]**	**X**	**X**	**X**	**X**	**X[c]**
Medical history	**X**					
Safety/toxicity (graded by CTCAE v5.0)	**X**	**X**	**X**	**X**	**X**	
Concomitant treatments	**X**	**X**	**X**	**X**	**X**	**X[c]**
PARACLINICAL EXAMINATION						
Tumor assessment (CT scan by RECIST v1.1)[d]	**X**	**X**	**X**	**X**	**X**	
Electrocardiogram (12-lead)	**X**					
BIOLOGICAL TESTS						
Complete blood count with differential	**X[2]**	**X**	**X[2]**	**X**	**X**	
Blood electrolytes: sodium, potassium, chloride, calcium, and phosphate)	**X[2]**	**X**	**X[2]**	**X**	**X**	
Liver function tests: AST, ALT, bilirubin (total and direct), alkaline phosphatase, and GGT	**X[2]**	**X[e]**	**X[2]**	**X[e]**	**X**	
Kidney function tests: creatinine (serum), and uric acid. Creatinine clearance estimated by Cockcroft-Gault equation.	**X[2]**	**X**	**X[2]**	**X**	**X**	
Proteinuria	**X[2]**	**X**	**X[2]**	**X**		
Pancreas function test: lipase, amylase	**X[2]**	**X**	**X[2]**	**X**	**X**	
Thyroid function tests: TSH, T3, and T4	**X[2]**	**X**	**X[2]**	**X**	**X**	
Coagulation panel: PT, INR, and PTT	**X[2]**	**X**	**X[2]**	**X**	**X**	
Pregnancy test (urine or serum)	**X[2]**					

VISITS	Baseline visit(s)	Visits during first treatment phase	Change of study treatment visit	Visits during the second treatment phase	Study treatment discontinuation visit	Long-term follow-up visits
Visit timelines	*≤28 days before starting treatment*	*On D1 of each 28-day treatment cycle*	*≤4 weeks delay between first and second treatment phases*	*On D1 of each 28-day treatment cycle*	*30±7 days after second treatment discontinuation*	*Every 3±1 months for 3 years and every 6±1 months for 2 years*
QUALITY OF LIFE						
QLQ-C30[f]	**X[2]**	**X**	**X**	**X**	**X**	
BIOLOGICAL SAMPLES ANCILLARY STUDIES (optional) – French sites only						
Collection of previously collected tumor samples	**X**					
Plasma samples (ctDNA + STC1)	ctDNA (2 tubes) + STC1 (1 tube)	ctDNA (2 tubes) (+STC1 at 1st CT-scan assessment – 1 tube)	ctDNA (2 tubes) (+ STC1 at progression – 1 tube)	ctDNA (2 tubes)	ctDNA (2 tubes) (+ STC1 at progression – 1 tube)	
Whole blood sample (gDNA)	gDNA (1 tube)					

[a]Height will only be collected at baseline;
[b]During regorafenib treatment blood pressure must be verified weekly during the first 6 weeks of treatment;
[c]Only survival data, ECOG PS and subsequent treatment if any will be collected during the long-term follow-up phase;
[d]Tumor assessments will be performed at baseline and then every 8 weeks (±7 days) until disease progression;
[e]During regorafenib treatment liver function tests (AST, ALT, and bilirubin [total and direct]) must be performed every 2 weeks for the first and second cycles;
[f]Completed at baseline, every 8 weeks during treatment, at the change of study treatment visit, and at the study treatment discontinuation visit.
[1]Must be performed within 14 days of starting the study treatment.
[2]Must be performed within 7 days of starting the study treatment.
D: day; ECOG PS: Eastern Cooperative Oncology Group performance status; CTCAE: common terminology criteria for adverse events; CT: computed tomography; RECIST: response evaluation criteria in solid tumours; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma-glutamyl transferase; TSH: thyroid-stimulating hormone; T3: free triiodothyronine; T4: free thyroxine; PT: prothrombin time; INR: international normalized ratio ; PTT: partial thromboplastin time, QLQ-C30: quality of life questionnaire C30.