A randomized phase III trial assessing a regorafenib-irinotecan combination (REGIRI) versus regorafenib alone in metastatic colorectal cancer patients after failure of standard therapies, according to the A/A genotype of Cyclin D1

NEXT-REGIRI

N°Study Sponsor	N°EudraCT
PROICM 2018-01 NEX	2018-002231-24
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CONFIDENTIAL

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Date & Name of CPP: IDF III, on 11/09/2018

ABBREVIATIONS

List of abbreviations	Explanation
5-FU	5 FluoroUracil
AE	Adverse Event
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/sGPT
ANC	Absolute neutrophil count
ANSM	Agence nationale de sécurité du médicament et des produits de santé (French National Agency fo Medicines and Health Products Safety)
AST	aspartate aminotransferase/glutamic oxaloacetic transaminase/sGOT
β-HCG	Beta human chorionic gonadotropin
BSA	Body surface area
CA 19-9	Carbohydrate Antigen 19-9
CCDN1	Cyclin D1
CEA	Carcino-Embryogenic Antigen
CPP	Ethic Comittee
CKD-EPI	Chronic Kindney Disease – Epidemiology Collaboration
CRA	Clinical Research Associate
CR	Complete response
CT Scan	Computed Tomography Scanner
DCF	Data clarification form
DCR	Disease control rate
ECG	ElectroCardioGram
ECOG	Eastern Cooperative Oncology Group
EOF	End of treatment
EORTC	European organisation for research and treatment of cancer
e-CRF	Case report form
EUDRACT	European Union Drug Regulating Authorities Clinical Trials
G-CSF	Granulocyte colony-stimulating factor
GGT	Gamma-glutamyl transferase
HB	Hemoglobin
HR	Hazard Ratio
HRQOL	Health-related quality of life
ICM	Montpellier Cancer Institute
ISC	Independent scientific committee
INCA	Institut national du cancer
INR	International Normalized Ratio
ITT	Intention-To-Treat
LDH	Lactate Dehydrogenase
mCRC	Metastatic colorectal cancer

MRI	Magnetic Resonance Imaging
NCI/ CTCAE	National Cancer Institute (US) Common terminology criteria for adverse events
NYHA	New-York Heart Association
PET-Scan	Positron emission tomography
PR	Partial response
PT	Prothrombin time
PTT	Partial Thromboplastin Time
RAS	Rat sarcoma viral oncogene homolog
RBC	Red Blood Count
RECIST	Response Evaluation Criteria in Solid Tumors
RS	Reference sequence
SAE	Serious Adverse Event
SD	Stable Disease
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TSH	Thyroid stimulating hormone
ULN	Upper limit normal
WBC	White Blood Count
WT	Wild type

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SYNOPSIS	
TITLE	**A randomized phase III trial assessing a regorafenib-irinotecan combination (REGIRI) versus regorafenib alone in metastatic colorectal cancer patients after failure of standard therapies, according to the A/A genotype of Cyclin D1**
SYNOPSIS VERSION	5.0
PATHOLOGY	Metastatic colorectal cancer
PROTOCOL CODES	**Acronym**: NEXT-REGIRI **Sponsor Code**: PROICM 2018-01 NEX **EUDRACT**: 2018-002231-24
STUDY SPONSOR	**ICM – Institut régional du cancer de Montpellier** Clinical, Translational and innovation Research Department Dr JP Bleuse 208 rue des Apothicaires 34298 Montpellier Cedex 05 – France Mail: DRCI-icm105@icm.unicancer.fr Phone: 04 67 61 31 02 Fax: 04 67 41 30 23
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STUDY DESIGN	Multicenter randomized Phase III study
NUMBER OF PLANNING PATIENT	78 patients out of about 312 screened patients

BACKGROUND AND RATIONALE	Patients with metastatic colorectal cancer (mCRC) who have received all approved standard treatments (except Regorafenib and TAS 102) no longer have treatment options available while maintaining a good performance status which would allow them to receive a new treatment. A Phase III randomized trial that compared Nexiri (Nexavar® + Irinotecan) vs irinotecan or versus Sorafenib alone showed a progression-free survival at two-months which was favorable to the NEXIRI combination ; 59% (IC95% : 39-66) versus 23% (IC95% : 10-33) and 22% (IC95%: 8-30) respectively. The patients treated with Irinotecan or Sorafenib alone could receive NEXIRI combination after progression and the progression-free survivals were 3,7 months (IC95% : 2,2-4,9) and 3,5 months (IC95% : 2,1-3,7) in patients treated with NEXIRI or after progression and 1,9 months (IC95% : 1,7-2,1) and 2,1 months (IC95% : 1,9-2,5) in patients treated only with Irinotecan and Sorafenib respectively. The median overall survival was higher with NEXIRI : 7,2 months (patients treated from the beginning of the study) and 7,9 months (patients treated after progression and crossover) versus 3 months in patients treated only with Irinotecan and 3,2 months in patients receiving only Sorafenib. The A870A rs603965 polymorphism of cyclin D1, a molecule involved in the initiation of cell division, was favorable to the NEXIRI combination on overall survival with a median of 19.6 months versus 6.2 months for two other genotypes A/G and G/G. Regorafenib, which is an oral signal deactivation agent with a chemical structure very similar to Sorafenib, is a standard treatment in heavily pretreated mCRC patients since the results of CORRECT study which compared Regorafenib to placebo on overall survival showed a superiority of Regorafenib : 6,4 months versus 5 months (HR 0,774 [IC95% 0,63, 0,94]). Sorafenib isn't approved in mCRC so the objective of this NEXT-REGIRI trial is compared REGIRI combination (Regorafenib-Irinotecan) to Regorafenib alone in a phase III trial in patients in progression after having received all standard treatments and bearing genotype A/A of cyclin D1.

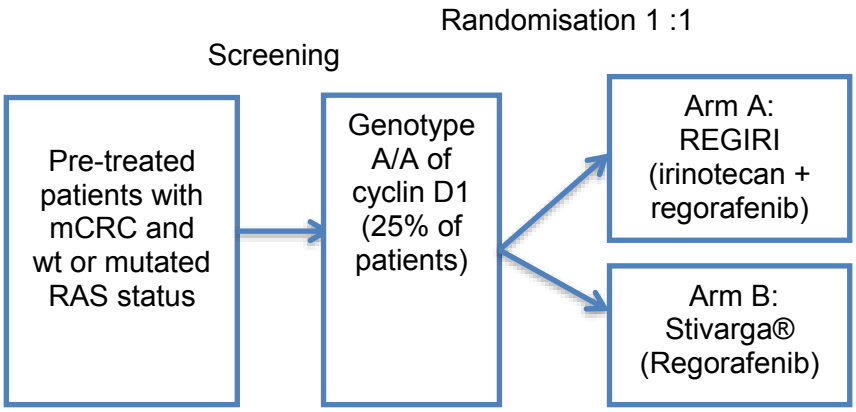
STUDY OBJECTIVES	**Primary objective** Comparison of overall survival in the Regorafenib and REGIRI combination (Regorafenib + Irinotecan) arms in mCRC patients of Cyclin D1 A/A genotype. **Secondary objectives** -Progression-free survival -Time to deterioration -Objective response rate -Disease control rate according to Recist criteria (version 1.1) -Toxicity (according to the NCI-CTCAE v5.0) -Quality of life (EORTC QLQ-C30)
STUDY ENDPOINTS	**Primary endpoint:** Overall survival presented with its median and confidence interval at 95%, estimated from randomization date to the date of death, whatever the cause, using the Kaplan-Meier method. **Secondary endpoints:** The secondary efficacy endpoint include: - Progression-free survival (PFS), defined as the time (days) from date of randomization 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. - Time to Deterioration is defined as the time between the date of randomization and the first time the patient has a WHO ≥ 2 during treatment. - Disease control rate (DCR), defined as the rate of patients, whose best response was not progressive disease (i.e., CR, PR or SD), to all randomized patients in the treatment group - Objective response rate (OOR), defined as the rate of patients with CR or PR, to all randomized patients in the treatment group. Patients prematurely discontinuing without an assessment will be considered non-responders for the analysis. - Safety will be evaluated using the NCI-CTCAE version 5.0 scale; at each visit for the duration of the treatment. -Quality of life will be evaluated, using the EORTC QLQ-C30 questionnaire. The expected benefit is an overall survival improvement of this treatment in patients with metastatic colorectal cancer who have received all standard treatments except TAS-102 and Regorafenib.

RISK AND BENEFITS	Toxicity and tolerance will be clinically and biologically assessed and rated on the NCIC CTCAE V5.0 scale at each visit. The expected benefit is an improvement in the overall survival of this treatment in patients with metastatic colorectal cancer who have received all standard treatments except TAS-102 and regorafenib. The risks of the study are continuously assessed by the MHI's pharmacovigilance department. This risk-benefit will be discussed in periodic safety reports. These reports will include all regulatory aspects and will be submitted to the competent authorities.
ELIGIBILITY CRITERIA	**Inclusion criteria** 1. Signed informed consent obtained before any study specific procedures 2. Male or female ≥ 18 years of age 3. Histological documentation of adenocarcinoma of the colon or rectum 4. Patients with metastatic colorectal cancer 5. Progression during or within 3 months following the last administration of approved standard therapies, which must include a fluoropyrimidine (or raltitrexed), oxaliplatin, irinotecan, anti-VEGF therapy and an anti-EGFR therapy (for RAS wild-type tumors), encorafenib 6. ECOG performance status ≤1 7. Life expectancy of at least 3 months 8. Patients with A/A CCND1 genotype of rs603965 CCND1 9. Adequate bone marrow, liver and renal function as assessed by the following laboratory requirements conducted within 7 days of starting study treatment: ➢ Lipase ≤ 1.5 x ULN ➢ Total bilirubin ≤ 1.5 x ULN ➢ Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3.0 x ULN (≤ 5 x ULN for patients with liver involvement of their cancer)

	➢ Alkaline phosphatase (ALP) ≤ 2.5 x ULN (≤ 5.0 x ULN for patients with liver involvement for their cancer and/or have bone metastases) ➢ Platelet count ≥ 100,000/mm3; Hemoglobin (Hb) ≥ 9 g/dL; Absolute neutrophil count (ANC) ≥ 1,500/ mm3. Transfusion to meet the inclusion criterion ➢ Serum creatinine ≤ 1.5 x ULN 10. International normalized ratio (INR) ≤ 1.5 x ULN and partial thromboplastin time (PTT) or activated partial thromboplastin time (aPTT) ≤ 1.5 x ULN unless receiving treatment with therapeutic anticoagulation. Patients being treated with anticoagulant, e.g., heparin, will be allowed to participate provided no prior evidence of an underlying abnormality in these parameters exists. Close monitoring of at least weekly evaluations will be performed until INR and PTT are stable based on a pre-dose measurement as defined by the local standard of care 11. Women of childbearing potential must have a blood or urine pregnancy test performed a maximum of 7 days before start of study treatment, and a negative result must be documented before start of study treatment 12. Women of childbearing potential and men must agree to use adequate contraception before entering the study until at least respectively 7 months and 4 months after the last study drug administration of Regorafenib and respectively 6 months and 3 months after the last study drug administration of Irinotecan. 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. **Exclusion criteria** 1. Patients with A/G or G/G CCND1 genotype of rs603965 CCND1 2. Prior treatment with regorafenib or sorafenib 3. Prior treatment with TAS 102 4. Major surgical procedure, open biopsy, or significant

	traumatic injury within 28 days before start of study drug 5. Pregnant or breast-feeding subjects. Women of childbearing potential must have a pregnancy test performed a maximum of 7 days before start of treatment, and a negative result must be documented before start of study drug 6. Congestive heart failure ≥ New York Heart Association (NYHA) class 2 7. Unstable angina (angina symptoms at rest), new-onset angina (begun within the last 3 months) 8. Myocardial infarction less than 6 months before start of study drug 9. Cardiac arrhythmias requiring anti-arrhythmic therapy (beta blockers or digoxin are permitted) 10. Uncontrolled hypertension. (Systolic blood pressure > 140 mmHg or diastolic pressure > 90 mmHg despite optimal medical management) 11. Pleural effusion or ascites that causes respiratory compromise (≥ NCI-CTCAE V5.0 Grade 2 dyspnea) 12. Ongoing infection > Grade 2 NCI-CTCAE V5.0 13. Known history of human immunodeficiency virus (HIV) infection 14. Active hepatitis B or C, or chronic hepatitis B or C requiring treatment with antiviral therapy 15. Patients with seizure disorder requiring medication 16. History of organ allograft 17. Patients with evidence or history of any bleeding diathesis, irrespective of severity 18. Any hemorrhage or bleeding event ≥ NCI-CTC V5.0 Grade 3 within 4 weeks prior to the start of study medication 19. Non-healing wound, ulcer, or bone fracture

	20. Dehydration NCI-CTCAE V5.0 Grade ≥ 1 21. Substance abuse, medical, psychological or social conditions that may interfere with the subject's participation in the study or evaluation of the study results 22. Known hypersensitivity to any of the study drugs, study drug classes, or excipients in the formulation 23. Any illness or medical conditions that are unstable or could jeopardize the safety of the subject and his/her compliance in the study 24. Persistent proteinuria of NCI-CTCAE V5.0 Grade 3 (> 3.5g/24 hours) 25. Patients unable to swallow oral medications 26. Any malabsorption condition 27. Chronic inflammatory bowel disease and / or bowel obstruction 28. Unresolved toxicity higher than NCI-CTCAE V.5.0 Grade 1 attributed to any prior therapy/procedure excluding alopecia, hypothyroidism and oxaliplatin induced neurotoxicity ≤ Grade 2 29. Concomitant participation or participation within the last 30 days in another clinical trial 30. Systemic anticancer therapy during this trial or within 4 weeks before randomization 31. Concomitant intake of St. John's wort 32. Live attenuated vaccines are prohibited 10 days before the treatment, during the treatment and 6 months after the termination of treatment 33. History of gastrointestinal fistula or perforation 34. 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)].
STUDY PRODUCT OR MEDICAL DEVICE	**REGORAFENIB** **IRINOTECAN**
ENROLLMENT PROCEDURE	
TREATMENT OR SURGERY MODALITIES	**Experimental arm : REGIRI (arm A)** -Irinotecan will be administered every 15 days. -1st cycle : Irinotecan will be administered at the dose of 120 mg/m² on D1 by a IV perfusion over 90 minutes. -2nd cycle : if no diarrheas grade > 1 and any other toxicities grade > 2 then the Irinotecan dose will be at 150 mg/m² and administered on D1 by IV infusion over 90 minutes. -From the third cycle : if no diarrheas grade > 1 and any other toxicity grade > 2 then the Irinotecan dose will be at 180 mg/m² and administered on D1 by IV infusion over 90 minutes. D1=D15 -Regorafenib will be given orally at a dose of 160 mg, once daily during on days 2–8 and 16–22 of each cycle, D1 = D28 ➔ A chemotherapy course = 15 days, 1 cycle = 4 weeks **Control arm : STIVARGA® (Regorafenib) (arm B)** -Regorafenib will be given orally at a dose of 160 mg once daily over 3 weeks followed by 1 week off, D1=D28. 1 cycle = 4 weeks

ANCILLARY STUDY	*Immunohistochemistry :* The expression of cyclin D1 protein will be sought by immunohistochemistry on tissue sections obtained from paraffin-embedded specimens. We will investigate any association between protein expression and response to treatment. In addition, depending on the progress of knowledge at the time of the study is completed, other biomarkers predictive of response to treatment can be explored by IHC on the same tumor blocks.
STATISTICAL CONSIDERATIONS	To show an increase of median overall survival from 7 to 15 months (30% to 57% rates, respectively), with a HR=0.47 and a power of 80% and alpha=5%, 55 events are required for the 78 patients to be randomized considering 15% additional patients for lost to follow-up. The A/A Cyclin D1 (A/A CCDN1) genotype accounting for 25% of the mCRC patients, a screening of 312 patients will be required before randomization which will be stratified BY RAS status. The inclusion period will last 64 months No interim analysis is planned.
STUDY PERIOD	❖ **First inclusion** : september 2019 ❖ **Inclusion period** : 64 months ❖ **End of the inclusion period**:January 2025 ❖ **Expected end of study**: June 2025 ❖ **Report :** December 2025

1. Background and rationale

Until recently, there were no treatment options available for patients with metastatic colorectal cancer who progress after all approved standard therapies, although many patients maintain a good performance status and could be candidates for further therapy.

The NEXIRI combination (sorafenib + irinotecan) showed promising results in heavily pretreated mCRC patients with KRAS mutated tumors (1). A randomized phase II study assessed this combination versus irinotecan or sorafenib as monotherapies, with possible cross-over to the NEXIRI arm at progression for patients treated with either monotherapy. The progression-free survival at two months, the primary objective of the study, was of 59%. The median progression-free survival was of 3.7 months (95% CI: 2.2-4.9) and 3.5 months (95% CI: 2.1-3.7) in the NEXIRI and cross-over arms, and of 1.9 (95% CI: 1.7-2.1) and 2.1 (95% CI: 1.9-2.5) in the irinotecan and sorafenib (monotherapies) groups, respectively. The median overall survival was higher in patients treated with NEXIRI, either from the beginning of the study or at progression (cross-over patients): 7.2 (95% CI: 5.8-9.4) and 7.9 months (95% CI: 7.1-8.7) compared with patients treated only with irinotecan or sorafenib, respectively 3 (95% CI: 2.1-3.8) and 3.3 months (95% CI: 2.5-4.2) (2).

Cyclin D1 (CCND1) is involved in the G1 phase of the cell cycle; the A870G rs603965 polymorphism is specifically associated with response to anti-cancer treatments (3,4). The A/A genotype, which generates a truncated form of CCND1, was favorable to the NEXIRI combination on overall survival, with a median of 19.6 months (95% CI: 4.8-/) versus 6.2 months (95% CI: 4.9-9.4) for the A/G and G/G genotypes; this benefit was not reported in patients treated with sorafenib alone.

This data would have warranted further investigation through a large, randomized phase III trial, however, information was given by Bayer that no clinical development was planned in the indication of mCRC with sorafenib.

Regorafenib is an oral tumor deactivation agent – whose chemical structure is close to that of sorafenib - which potently blocks multiple protein kinases, including kinases involved in tumor angiogenesis, oncogenesis, metastasis and tumor immunity. Unlike sorafenib, regorafenib underwent a clinical development program in GI cancers, showing survival benefits in metastatic colorectal cancer which has progressed after all standard therapies. In the phase III study CORRECT, the addition of regorafenib to best supportive care resulted in significantly longer survival, compared to placebo plus best supportive care, with a p value of 0.005178 from stratified log rank test, a hazard ratio of 0.774 [95% CI 0.636, 0.942]) and a median OS of 6.4 months vs. 5.0 months (5). This study provided evidence for a continuing role of targeted treatment after disease progression, with regorafenib offering a potential new line of therapy in this treatment-refractory population.

Meanwhile, a combination approach was investigated to create potential synergy with the ultimate objective to improve even more survival outcomes in this particular population.
A combination of FOLFOX or FOLFIRI (oxaliplatin 85 mg/m2 or irinotecan 180 mg/m2, D/L-folinic acid 400 mg/m2, 5-FU bolus 400 mg/m2 followed by 5-FU 2400 mg/m2 for 46 hours) every 2 weeks and regorafenib (160 mg/day administered sequentially to FOLFIRI on days 4-10 and 18-24 of every 4 week cycle, was explored in a phase Ib trial in patients with metastatic colorectal cancer (mCRC) (6). The incidence of drug-related adverse events of any grade was similar (no significant differences) between FOLFOX and FOLFIRI groups indeed Thrombocytopenia (20% vs 20%), Neutropenia was (44% vs 55%), Diarrhea (52% vs 60 %), hand-foot reaction skin reaction (36% vs 35%). The most frequent drug-related adverse events leading to dose modification were neutropenia (*n* = 12; 27%), mucositis (*n* = 8; 18%), hand–foot skin reaction (*n* = 8; 18%), and leukopenia (*n* = 5; 11%). Regorafenib in combination with mFOLFOX6 or FOLFIRI showed encouraging anti-tumor efficacy with partial response in 7 patients, 4 on regorafenib with mFOLFOX6 and 3 on regorafenib with FOLFIRI. Overall, disease control (i.e., partial response or stable disease) was achieved in 33 patients (87%), 18 on regorafenib with mFOLFOX6 and 15 on regorafenib with FOLFIRI. Even though regorafenib increased the exposure to SN-38 in the FOLFIRI group, it was not associated with reduced tolerability.
These findings were confirmed in a multicenter, randomized, double-blind phase II trial of FOLFIRI plus regorafenib (A) or FOLFIRI + placebo (B) in mCRC, in which the addition of regorafenib on an intermittent schedule (week on, week off) to FOLFIRI as 2nd line therapy, was tolerable, and resulted in a statistically significant prolongation of PFS compared to FOLFIRI alone. Grade ≥ 3 adverse events occurring in > 5% of patients (A vs B) included neutropenia (40% vs 30%), diarrhea (14% vs 5%), hypophosphatemia (14% vs 0%), fatigue (11% vs 7%), mucositis (9% vs 10%), hypertension (8% vs 2%), elevated lipase (8% vs 3%) and hand-foot syndrome was grade ≥ 5% on arm A vs 2% on B. The addition of regorafenib on an intermittent schedule to FOLFIRI was tolerable, and resulted in a statistically significant prolongation of PFS compared to FOLFIRI alone (7).

Altogether, these results and those of the NEXIRI study justify conducting a phase III randomized trial assessing a regorafenib – irinotecan (REGIRI) combination versus Regorafenib alone in mCRC patients of CCND1 A/A genotype, who have progressed being treated with available therapies.

2. Study objectives and Endpoints

2.1 Objectives

2.1.1 Primary objective

Comparison of overall survival in the Regorafenib and REGIRI combination (Regorafenib + Irinotecan) arms in mCRC patients of Cyclin D1 A/A genotype.

2.1.2 Secondary objective

- Progression-free survival
- Time to deterioration
- Objective response rate
- Disease control
- Toxicity (according to the NCI CTC V5.0)
- Quality of life (EORTC QLQ-C30 – appendix 2)

2.2 Endpoints

2.2.1 Primary endpoint

Median Overall survival presented with its confidence interval at 95%, estimated from the randomization date to the date of death, whatever the cause, using the Kaplan-Meier method.

2.2.2 Secondary endpoints

The secondary efficacy endpoints include:

- Progression-free survival (PFS), defined as the time (days) from date of randomization 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.
- Time to Deterioration is defined as the time between the date of randomization and the first time the patient has a WHO ≥ 2 during treatment.
- Disease control rate (DCR), defined as the rate of patients, whose best response was not progressive disease (i.e., CR, PR or SD), to all randomized patients in the treatment group- Objective response rate (OOR), defined as the rate of patients with CR or PR, to all randomized patients in the treatment group. Patients prematurely discontinuing without an assessment will be considered non-responders for the analysis.

- Safety will be evaluated by clinical and biological means and scored on the NCI-CTCAE version 5.0 scale, performed at each visit (every 2 weeks).

-Quality of life will be evaluated, based on the EORTC QLQ-C30 questionnaire (appendix 2).

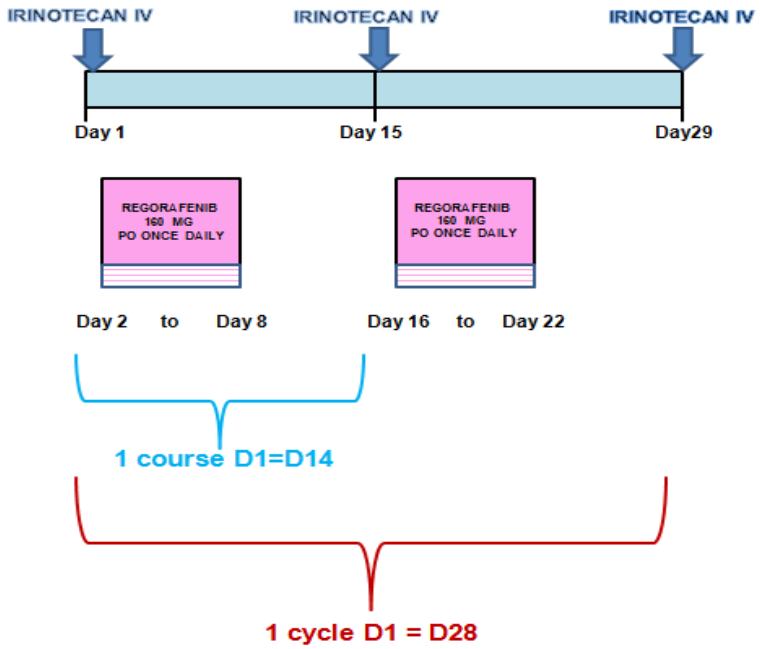
3. Experimental plan

3.1 Study design

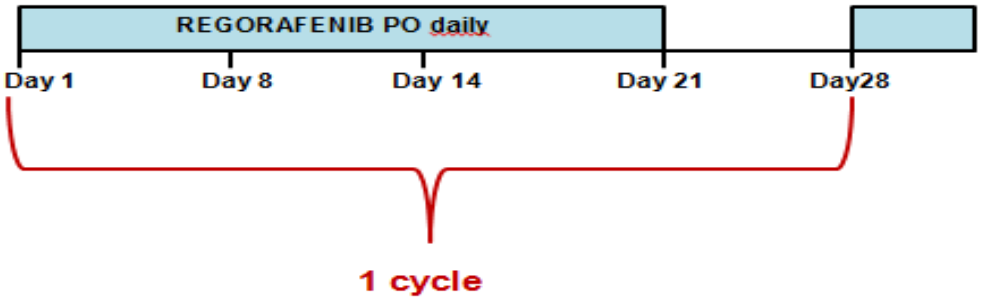
This is an open, prospective, multicenter, randomized Phase III study.

78 patients will be randomized in several centers.

Experimental arm : REGIRI (arm A)



Control arm : Stivarga® (Regorafenib) (arm B)



- **First inclusion** : september 2019
- **Inclusion period** : 64 months
- **End of the inclusion period**: January 2025
- **Expected end of study**: June 2025
- **Report :** December 2025

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

-78 patients randomized out of approximately 312 screened patients.

-Patients with wild-type or mutated RAS status and Genotype A/A of cyclin D1 (25% of patients).

4.2 Inclusion criteria

1. Signed informed consent obtained before any study specific procedures
2. Male or female ≥ 18 years of age
3. Histological documentation of adenocarcinoma of the colon or rectum
4. Patients with metastatic colorectal cancer
5. Progression during or within 3 months following the last administration of approved standard therapies, which must include a fluoropyrimidine (or raltitrexed), oxaliplatin, irinotecan, anti-VEGF therapy and an anti-EGFR therapy (for RAS wild-type tumors), encorafenib
6. ECOG performance status ≤1
7. Life expectancy of at least 3 months
8. Patients with A/A CCND1 genotype of rs603965 CCND1
9. Adequate bone marrow, liver and renal function as assessed by the following laboratory requirements conducted within 7 days of starting study treatment:

- Lipasémie ≤1.5 x ULN
- Total bilirubin ≤ 1.5 x ULN
- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3.0 x ULN (≤ 5 x ULN for patients with liver involvement of their cancer)
- Alkaline phosphatase (ALP) ≤ 2.5 x ULN (≤ 5.0 x ULN for patients with liver involvement for their cancer and/or have bone metastases)
- Platelet count ≥ 100,000/mm3; Hemoglobin (Hb) ≥ 9 g/dL; Absolute neutrophil count (ANC) ≥ 1,500/ mm3. Transfusion to meet the inclusion criterion will not be allowed
- Serum creatinine ≤ 1.5 x ULN

10. International normalized ratio (INR) ≤ 1.5 x ULN and partial thromboplastin time (PTT) or activated partial thromboplastin time (aPTT) ≤ 1.5 x ULN unless receiving treatment with therapeutic anticoagulation. Patients being treated with anticoagulant, e.g., heparin, will be allowed to participate provided no prior evidence of an underlying abnormality in these parameters exists. Close monitoring of at least weekly evaluations will be performed until INR and PTT are stable based on a pre-dose measurement as defined by the local standard of care
11. Women of childbearing potential must have a blood or urine pregnancy test performed a maximum of 7 days before start of study treatment, and a negative result must be documented before start of study treatment
12. Women of childbearing potential and men must agree to use adequate contraception before entering the study until at least respectively 7 months and 4 months after the last study drug administration of Regorafenib and respectively 6 months and 3 months after the last study drug administration of Irinotecan. 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.

4.3 Non-inclusion criteria

1. Patients with A/G or G/G CCND1 genotype of rs603965 CCND1
2. Prior treatment with regorafenib or sorafenib
3. Prior treatment with TAS 102
4. Major surgical procedure, open biopsy, or significant traumatic injury within 28 days before start of study drug
5. Pregnant or breast-feeding subjects. Women of childbearing potential must have a pregnancy test performed a maximum of 7 days before start of treatment, and a negative result must be documented before start of study drug
6. Congestive heart failure ≥ New York Heart Association (NYHA) class 2 (appendix 3)
7. Unstable angina (angina symptoms at rest), new-onset angina (begun within the last 3 months)
8. Myocardial infarction less than 6 months before start of study drug
9. Cardiac arrhythmias requiring anti-arrhythmic therapy (beta blockers or digoxin are permitted)
10. Uncontrolled hypertension. (Systolic blood pressure > 140 mmHg or diastolic pressure > 90 mmHg despite optimal medical management)
11. Pleural effusion or ascites that causes respiratory compromise (≥ CTCAE Grade 2 dyspnea)
12. Ongoing infection > Grade 2 CTCAE V5.0
13. Known history of human immunodeficiency virus (HIV) infection
14. Active hepatitis B or C, or chronic hepatitis B or C requiring treatment with antiviral therapy
15. Patients with seizure disorder requiring medication
16. History of organ allograft
17. Patients with evidence or history of any bleeding diathesis, irrespective of severity
18. Any hemorrhage or bleeding event ≥ CTCAE Grade 3 within 4 weeks prior to the start of study medication
19. Non-healing wound, ulcer, or bone fracture

20. Dehydration CTCAE V5.0 Grade ≥ 1

21. Substance abuse, medical, psychological or social conditions that may interfere with the subject's participation in the study or evaluation of the study results

22. Known hypersensitivity to any of the study drugs, study drug classes, or excipients in the formulation

23. Any illness or medical conditions that are unstable or could jeopardize the safety of the subject and his/her compliance in the study

24. Persistent proteinuria of CTCAE Grade 3 (> 3.5g/24 hours)

25. Patients unable to swallow oral medications

26. Any malabsorption condition

27. Chronic inflammatory bowel disease and / or bowel obstruction

28. Unresolved toxicity higher than CTCAE (V5.0) Grade 1 attributed to any prior therapy/procedure excluding alopecia, hypothyroidism and oxaliplatin induced neurotoxicity ≤ Grade 2

29. Concomitant participation or participation within the last 30 days in another clinical trial

30. Systemic anticancer therapy during this trial or within 4 weeks before randomization

31. Concomitant intake of St. John's wort

32. Live attenuated vaccines are prohibited 10 days before the treatment, during the treatment and 6 months after the termination of treatment

33. History of gastrointestinal fistula or perforation

34. 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 bladder tumors [Ta (non invasive tumor), Tis (carcinoma superficial in situ and T1 (lamina propria invasion)

4.4 Procedure

Enrollment procedures will be performed using Electronic Case report Form (eCRF).

The procedure of use of eCRF for randomization will be given to all investigators during the study opening of each of the centers.

This enrolment procedure will be performed in 2 steps:

1/ Inclusion (screening): After inclusion and non-inclusion criteria have been fulfilled and the patient consent has been obtained, the patient will be included in the trial.
2/ Randomization: The randomization procedure will allocate the treatments A or B using list algorithm, with a 1:1 ratio and will be stratified by the following criteria:
-RAS Status

The inclusion / randomization will be performed using the module of the eCRF / Ennov Clinical® software. After the consent form has been signed and all inclusion/ non-inclusion criteria checked, the investigator will proceed with the randomization through the ICM online e-CRF:

https://ecrfcval.icm.unicancer.fr/CSOnline/

An automatic reply will be sent by e-mail to confirm the success of the randomization 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 NEXT-REGIRI	Screening					Treatment						Evaluation (Every 8 weeks)	End of treatment [b,c]	Safety Follow-up[c,d]	Follow-up	End of study
						Regorafenib (1 cycle = 4 weeks		REGIRI (1 course = every 15 days and 1 cycle = every 4 weeks)								
Baseline Documentation	**As early as second-line**	**~ 28 days**	**Within 28 days**	**Within 14 days**	**Within 7 days**	**CX D1[a]**	**C1, C2 D8**	**CX D1[a]**	**C1, C2 D8**	**Cx D15**	**C1, C2 D22**	**~8 weeks**	**~14 days**	**~30 days**	**Follow-up: every other month**	
Molecular testing informed consent	X															
Clinical trial informed consent			X													
Complete medical history			X													
Inclusion/Exclusion Criteria checked			X													
Physical examination					X	X		X		X			X			
β-HCG blood test					X	X		X								
Status of Ras, Raf and MSI have to be known		X														
Laboratory Studies																
12-lead ECG					X	X[1]		X[1]				X	X[4]			
Complete blood count					X	X		X		X			X[4]			
Coagulation					X	X		X		X			X[4]			
Electrolyte panel					X	X		X		X			X[4]			
Chemistry panel					X	X		X		X			X[4]			

Tabulated overview NEXT-REGIRI	Screening				Treatment						Every 8 weeks	End of treatment [b,c]	SafetyFollow-up[c-d]	Follow-up	End of study
					Regorafenib (1 cycle = 4 weeks		REGIRI (1 course = every 15 days and 1 cycle = every 4 weeks)								
Liver function test panel				X	X[2]		X	X	X	X		X[4]			
Thyroid function				X	X		X					X[4]			
Tumor markers				X	X[3]		X[3]				X	X[4]	X[5]		
Urinary analysis				X	X		X		X			X[4]			
Imaging assessments															
Radiologic Tumor assessment [d]		X									X	X[6]	X[5]		
Other Clinical Assessments															
ECOG				X	X		X		X			X[4]			
Body weight, BSA, height, and vital signs				X	X		X	X[7]	X			X[4]			
Concomitant medications			X		X		X		X			X	X		
Adverse events				X	X		X	X	X	X		X	X		
Drug dispensing					X[8]		X[8]								
Drug accountability					X[8]		X[8]		X			X			
Post-study survival status														X	
Anti-cancer medications														X	
Patient's diary					X[9]		X[9]		X						
Patient Reported Outcomes															
Quality of life questionnaires					X[10]		X[10]				X				
Phone call : adverse events, blood pressure					X	X				X					
Ancillary study															
Immunohistochemistry[e]															X

a: Cycle 1 Day 1 : the laboratory evaluations are not required at day 1 of cycle 1 if those were completed within 7 days

b: Within 14 days (+/- 7 day) after study treatment has stopped

c: Within 30 days (+/- 7 day) after study treatment has stopped

d: CT scan of the abdomen, pelvis and chest or hepatic MRI and CT scan of the pelvis and chest without injection; RECIST criteria version 1.1

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

1: A 12-lead ECG will be performed at the end of every other cycle (8 weeks, if there's no postponed treatment)

2 : D1 and D15 of the first two cycles for Bras B (Stivarga®) and D1 only at the other cycles

3: Tumor markers CEA and CA 19-9 at every cycle

4: If the last clinical and laboratory evaluations > 7 days

5: if not done at the EOT visit

6: If the last radiological tumor assessment > 1 month

7: C1-C2 D8 (arm A) : vital signs without height, weight and BSA

8: As applicable

9: A treatment diary will be handed over to patient on cycle 1 day 1

10: EORTC QLQ-C30 questionnaires will be completed by the patient on Day 1 of Cycle 1 then at each evaluation (= 8 weeks) for both treatments

5.2 Screening period

Enrollment into NEXT-REGIRI will be performed in two stages with two separate informed consent forms. Initially, all potential patients will consent to undergo molecular testing (appendix 4). The blood sample for molecular testing will be sent off to :

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 molecular testing will be carried out by Dr Evelyne Crapez.

Dr Evelyne Crapez
Responsable de l'unité de recherche translationnelle
Institut régional du cancer de Montpellier

Unité de recherche translationnelle
208, rue des Apothicaires – Parc Euromedecine
34298 Montpellier CEDEX 5
Tel : +33 (0) 4.67.61.30.48 – Fax : +33 (0) 4.67.41.08.59
Evelyne.Crapez@icm.unicancer.fr

Only patients with the Sequence A/A rs603965 of cycline D1 gene can be screened for the study treatment (REGIRI vs Regorafenib). A second consent form to screen for the clinical study (Clinical Trial Consent).
Both consent processes are independent of each other.

The following procedure will be able to be performed as early as second-line treatment**:**

- A blood sample will be collected into a PAXGENE DNA tube then will be shipped to CRB-ICM for determining the variant A/A genotype of cyclin D1

The following procedures and assessments will be performed **around 28 days of starting study Drug for both arms of treatment:**

- Status of RAS, RAF and MSI have to be known

- Obtainment of molecular testing informed consent

The following procedures and assessments will be performed **within 28 days of starting study Drug for both arms of treatment:**

- Obtainment of written informed consent. No screening procedures may be performed unless written informed consent has been obtained

- Inclusion/Exclusion criteria checked

- Radiological tumor assessment using the RECIST criteria, version 1.1 (see Appendix 5) 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)

- Complete medical history including demographics, allergies, prior surgery and prior chemo/radiation therapy with documentation of treatment response.

The following procedures and assessments will be performed **within 14 days of starting study drug:**

- Record of all concomitant medications except Homeopathy. All medicines and significant non-drug therapies taken within 14 days before study treatment must be recorded in the e-CRF.

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

- 12-lead ECG

- ECOG performance status (Appendix 6)

- Adverse events

- Physical examination including review of all organ systems, examination of pertinent organ systems, vital signs (heart rate, blood pressure, weight, BSA and height).
  The blood pressure measurements must be performed in a consistent manner using a manual cuff on the same arm. The assessment must be made with the patients in the sitting position using the same arm for all evaluations. Two additional measurements, taken 5 minutes apart, should be conducted if the first blood pressure is abnormal

- 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

- Electrolyte panel: sodium, potassium, calcium, chloride

- Chemistry panel: albumin, lipase, phosphate, glucose, serum creatinine, clearance calculated according CKD-EPI (appendix 7)

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

- Thyroid function test: TSH, free T3, and free T4

- Coagulation panel: Prothrombin time (PT) or the International Ratio of PT (PT-INR) and Partial Thromboplastin Time (PTT)

- Urine analysis: Urine analysis by urinary dipstick. If results of protein ≥ 3+, quantification of proteinuria on a 24-hour urine collection

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

- 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.

5.3 Treatment period

<u>REGIRI or Regorafenib:</u>

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

The following assessments should be performed on the first day and day 15 of each cycle (REGIRI) or cycle (Regorafenib) except C1D1 prior to receiving study treatment (+/- 3 days):

- 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) and vital signs (heart rate, blood pressure)
- 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 every other cycle (8 weeks if there's no postponed treatment) for both arms

- 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 and 15 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)

    ➔ Electrolyte panel: sodium, potassium, chloride, calcium

    ➔ Chemistry panel : albumin, lipase, phosphate, glucose, serum creatinine, clearance calculated according CKD-EPI (appendix 7)

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

➔ Thyroid function test (TSH, free T3, free T4, on day 1 of each cycle for both arms)

- Tumor markers CEA (Carcino-Embryogenic Antigen), CA 19-9 (carbohydrate Antigen 19-9) every cycle for both treatments

- 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 (on day 1 of each cycle for both arms).

- Urine analysis by urinary dipstick. If results of protein ≥ 3+, then quantification of proteinuria on a 24-hour urine collection must be done.

- EORTC QLQ-C30 (appendix 2) questionnaires will be completed by the patient on Day 1 of Cycle 1 (baseline) then on the first day of every other cycle (every 8 weeks)

- 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 arm A (REGIRI) and B (Regorafenib) of each cycle

Provide patient's diary on C1D1. It will allow to patient to write down his oral intakes and blood pressure values

The blood pressure must be monitored weekly for the first six weeks of study treatment.
The blood pressure will be recorded by the patient and entered onto his treatment diary. In the latter case, the patient should be instructed to contact the physician in the event of systolic ≥ 150 mm Hg and / or diastolic ≥ 100 mm Hg. The physician should confirm the reading before recording it into the e-CRF. Blood pressure measurements will be performed in patients sitting for 5 minutes prior to the evaluation. The patient should be instructed to take their blood pressure in the morning and repeat two more times for accuracy.

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

REGIRI (arm A)

- Vital signs (Heart rate and blood pressure)
- these laboratory evaluations are required: Aspartate Amino-Transferase (AST), Alanine Amino-Transferase (ALT), bilirubin (total and direct)

Stivarga® (Regorafenib) (arm B):

- Phone call by a treatment nurse for knowing if there are any adverse events and blood pressure value (current state of the art)

The following assessments should be performed on day 15 of cycle 1 and 2:

REGIRI (arm A)

- Physical examination with weight and vital signs (heart rate, blood pressure)
- ECOG performance status
- Concomitant medications (including start/stop dates, dose, indication)
- Adverse events documentation (including Start/Stop dates, seriousness, CTC notation and grading, relationship to study drug, outcome and action taken) using CTCAE V5.0
- 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, chloride, calcium

- Chemistry panel : albumin, lipase, phosphate, glucose, serum creatinine, clearance calculated according CKD-EPI (appendix 7)

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

- Urine analysis by urinary dipstick. If results of protein ≥ 3+, then quantification of proteinuria on a 24-hour urine collection must be done.

- Drug accountability (pharmacy)
  Verify patient's diary. It will allow to patient to write down his oral intakes and blood pressure values

The following assessments should be performed on day 15 of cycle 1 and 2:

Stivarga® (Regorafenib - arm B):

- these laboratory evaluations are required: Aspartate Amino-Transferase (AST), Alanine Amino-Transferase (ALT), bilirubin (total and direct)

The following assessments should be performed on day 22 of cycle 1 and 2:

REGIRI (arm A):

- Phone call by a treatment nurse for knowing if there are any adverse events and blood pressure value (current state of the art)
- These laboratory evaluations are required: Aspartate Amino-Transferase (AST), Alanine Amino-Transferase (ALT), bilirubin (total and direct)

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

REGIRI or Regorafenib:

- 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 5) 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. Throughout the study, the identical lesions to those identified and measured at baseline must be evaluated using the same technique, and preferably by the same radiologist. Copies of all CT scans performed for tumor assessment in non-progressive enrolled patients will be stored on CDs at the site

- EORTC QLQ-C30 (appendix 2) questionnaires will be completed by the patient at each evaluation i.e 8 weeks

5.4 End of treatment Visit

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 and vital signs (heart rate, blood pressure)

- 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, chloride and calcium

- Chemistry panel: albumin, lipase, phosphate, glucose, serum, creatinine, clearance calculated according CKD-EPI (appendix 7)

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

- Thyroid function test : TSH, free T3, and free T4

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

- Urine analysis by urinary dipstick. If results of protein ≥ 3, then quantification of proteinuria on a 24-hour urine collection must be done

- A radiological tumor assessment using the RECIST criteria, version 1.1 (see Appendix 5) 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)

- Drug accountability (pharmacy)

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:

- A radiological tumor assessment using the RECIST criteria, version 1.1 (see Appendix 5) 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

Follow-up every other month until Death

- Vital status
- Anti-cancer medications

Telephone follow-up is acceptable. Site staff must use caution when contacting the patient's family for this information, especially if they are no longer under the care of the investigator, so as to not inadvertently cause any distress to the family of a patient who is no longer alive.

6. Treatments

6.1 Experimental treatment or procedures

Experimental arm: REGIRI (arm A)

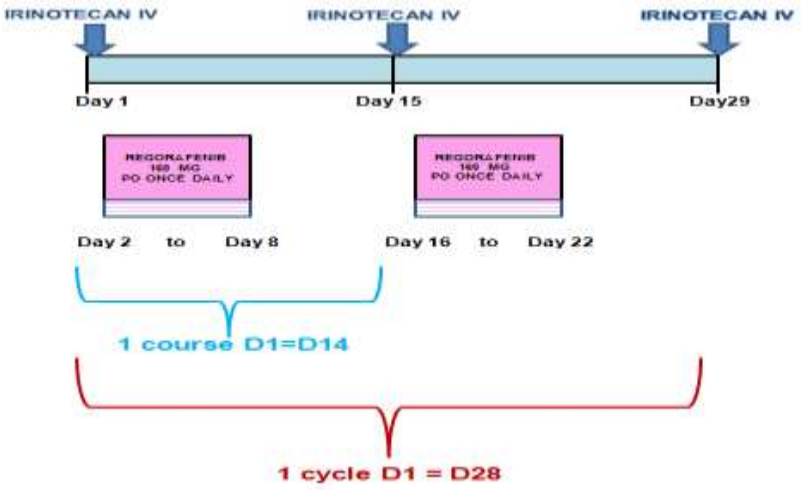


Figure 1 : REGIRI regimen

The treatment schedule will be as follows:

- Starting on days 1 and 15 of each 28-day cycle, all patients will receive irinotecan as an intravenous infusion over a 90 minute period.
The initial dose of irinotecan will be 120 mg/m^2.
The dose for the second infusion of irinotecan will be 150 mg/m^2 over 90 minutes if no diarrhea of grade >1 NCI-CTCAE V 5.0 grading or others toxicities of grade >2 occur.
The dose for the third and subsequent infusions of irinotecan will be 180 mg/m^2 over 90 minutes under the same conditions as for the 2nd infusion.

-On days 2–8 and 16–22 of each cycle, all patients will receive Regorafenib 160 mg orally once daily.

-A chemotherapy course = 15 days, 1 cycle = 4 weeks

Control arm: Stivarga® (Regorafenib) (arm B)

-Regorafenib will be given orally at a dose of 160 mg once daily over 3 weeks then one week off.
1 cycle = 4 weeks

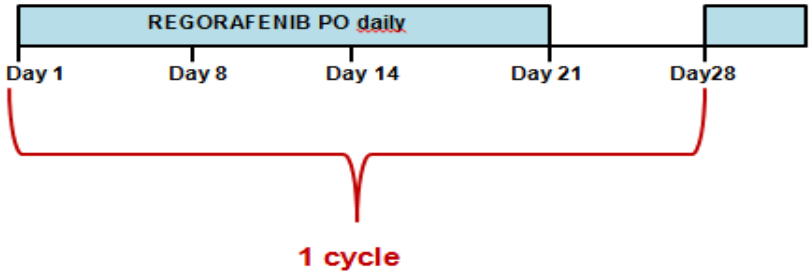


Figure 2: Regorafenib schedule

The following products will be used in the study:

- Regorafenib, 40 mg tablets
- Irinotecan, 180 mg/m² IV (20 mg/ml)

ARM A : REGIRI (Regorafenib + Irinotecan)

Irinotecan

See manufacturer's product information (Appendix 8).

Irinotecan will be prescribed by each center and used in its marketed form.

The irinotecan will be diluted in a 5 % glucose solution or a 0.9% sodium chloride solution. The irinotecan will be delivered over 90 minutes as an intravenous infusion.

Regorafenib

For Packaging, List of excipients and Storage: See Investigator's brochure (Appendix 8).

Regorafenib® will be provided by Sponsor as tablets of 40 mg.

The investigational product(s) label will bear sponsor's name, address and telephone number, the EudraCT number, product name, dosage form and strength, quantity of investigational product par container, batch number, expiration date, dosing instructions, required storage conditions and required caution statements and/or regulatory statements as applicable.

Receipt, distribution, return and destruction (if any) of the study drug must be properly documented.

To have complete control over the distribution and use of the study drug, the drug accountability must be performed on Day 1 of each cycle starting on Cycle 2. Bottles must be returned to the Investigator with all unused medication. Throughout the study, all unused study medication will be accounted for. The information will be recorded in the drug dispensing log.

The study drug 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. Our partner Bayer will send Regorafenib to Sodia which deliver Regorafenib to the investigational site's pharmacy on behalf of sponsor. The renewal of the Regorafenib must be requested by fax or e-mail to Sodia by the investigator center.

Regorafenib will be orally administered. It must not be chewed or smashed.
It should be taken once daily in the morning from day 2 to day 8 and day 16 to day 22 of cycle, at the same hour as possible, with approximately 200 mL of water. The Regorafenib can be administered after a low-fat (<30% fat) meal.

The Investigator or designated study personnel is responsible for dispensing the study drug to patients.

ARM B: Stivarga® (Regorafenib)

See manufacturer's product information (Appendix 8).

Stivarga® will be delivered in retail pharmacies and used in its marketed form.

To have complete control over the use of the study drug, the drug accountability must be performed on Day 1 of each cycle starting on Cycle 2. Bottles must be returned to the Investigator with all unused medication. Throughout the study, all unused study medication will be accounted for Investigator or pharmacist.
Regorafenib will be orally administered. It must not be chewed or smashed.

It should be taken once daily in the morning during the first 21 days of cycle, at the same hour as possible, with approximately 200 mL of water. The Stivarga® (Regorafenib) should be administered after a low-fat (<30% fat) breakfast.

6.2 Expected Toxicities

The expected adverse events of Irinotecan, and Regorafenib are described in the respective Summaries of Product Characteristics (SmPC). Refer to the latest current version on the public drug database website (Appendix 8) for:

- Stivarga® in the Regorafenib alone arm
- Irinotecan in the REGIRI arm

Refer to the latest investigator's brochure for Regorafenib in the REGIRI arm.

6.3 Dose modification and Dose delay

ARM A: REGIRI

Regorafenib : Dosage changes should be made in 40 mg increments (1 tablet). The recommended daily dose of Regorafenib is 160 mg.

Dose reductions of Regorafenib
1st reduction : 120 mg
2nd reduction : 80 mg

Table a*

Digestive toxicity : Diarrhea

A symptomatic treatment of the diarrhea occurring more than 24 hours after the irinotecan administration is possible by diosmectite (Smecta®), 1 sachet/8h and loperamide (Imodium®), 2 capsules/8h until 24 hours after the last stool which is loose or watery. If, in spite of this treatment, the diarrhea is not under control in the first 24 hours then fluoroquinolones as antibiotics will be orally given during 7 days.

In case of diarrhea > grade 1, the patient will receive during the next courses of treatment a prophylactic treatment by sucralfate (Keal®) 1 sachet / 6 h et Ercefuryl® 200 at a rate of 3 capsules/24 h.

Table 1: Action and dose modification during the administration of Irinotecan and Regorafenib after the first course of treatment in case of diarrhea

Grade	During the course of treatment	dose at the next course of treatment
Grade 1	NA	Irinotecan at 150 mg/m². Regorafenib at 160 mg per day + prophylactic treatment
Grade 2	Interrupt irinotecan until diarrhea resolves to Grade ≤ 1	Irinotecan at 120 mg/m². Regorafenib at 160 mg per day + prophylactic treatment
Grade 3	Interrupt irinotecan until diarrhea resolves to Grade ≤ 1	Irinotecan at 120 mg/m² and Regorafenib at 120 mg per day
Grade 4	Discontinue treatment permanently	Discontinue treatment permanently

Table 2: Action and dose modification during the administration of Irinotecan and Regorafenib after the second course in case of diarrhea

Grade	During the course of treatment	Dose at the third course of treatment
Grade 1	NA	Dose-escalation of irinotecan is permitted. Regorafenib at 160 mg per day + prophylactic treatment
Grade 2	Interrupt irinotecan until diarrhea resolves to Grade ≤ 1	Dose-escalation of irinotecan is not permitted. Regorafenib at 160 mg per day + prophylactic treatment
Grade 3	1st occurrence: Interrupt irinotecan until diarrhea resolves to Grade ≤ 1	1st occurrence: Decrease Irinotecan to 120 mg/m². Regorafenib to 160 mg per day

	2nd occurrence: Interrupt irinotecan until diarrhea resolves to Grade ≤ 1	2nd occurrence: Irinotecan dose is not changed at 120 mg/m² and decrease Regorafenib to 120 mg per day
	3rd occurence : Discontinue treatment permanently	3rd occurence : Discontinue treatment permanently
Grade 4	Discontinue treatment permanently	Discontinue treatment permanently

Table 3: Action and dose modification during the administration of Irinotecan and Regorafenib after the third course and beyond in case of diarrhea

Grade		During the course of treatment	Dose at the third course of treatment
Grade 1-2		Interrupt irinotecan until diarrhea resolves to Grade ≤ 1	No dose modification + prophylactic treatment
Grade 3	Patients having received the irinotecan dose of 180 mg/m2	1st occurrence: Interrupt irinotecan until diarrhea resolves to Grade ≤ 1 2nd occurrence: Interrupt irinotecan until diarrhea resolves to Grade ≤ 1	1st occurrence: Decrease Irinotecan to 150 mg/m². Regorafenib to 160 mg per day 2nd occurrence: Decrease Irinotecan to 120 mg/m². Regorafenib to 160 mg per day
		3rd occurence : Interrupt irinotecan until diarrhea resolves to Grade ≤ 1	3rd occurrence: Irinotecan is not changed at 120 mg/m² and decrease Regorafenib to 120 mg per day

		4th occurence : Discontinue treatment permanently	4th occurrence: Discontinue treatment permanently
	Patients having received the irinotecan dose of 150 mg/m^2	1st occurrence: Interrupt irinotecan until diarrhea resolves to Grade ≤ 1	1st occurrence: Decrease Irinotecan to 120 mg/m². Regorafenib to 160 mg per day
		2nd occurrence: Interrupt irinotecan until diarrhea resolves to Grade ≤ 1	2nd occurrence: Irinotecan is not changed at 120 mg/m² and decrease Regorafenib to 120 mg per day
		3rd occurence : Discontinue treatment permanently	3rd occurence : Discontinue treatment permanently
	Patients having received the irinotecan dose of 120 mg/m^2	1st occurrence: Interrupt irinotecan until diarrhea resolves to Grade ≤ 1	1st occurrence: Irinotecan is not changed at 120 mg/m² and decrease Regorafenib to 120 mg per day
		2nd occurrence: Discontinue treatment permanently	2nd occurrence: Discontinue treatment permanently
Grade 4		Discontinue treatment permanently	Discontinue treatment permanently

Hematologic toxicity

Table 4: Action and dose modification during the administration of Irinotecan in case of hematologic toxicity

CBC at D15	Delayed Treatment	Decrease the dose for the next courses of treatment
ANC < 1500/mm^3	J21*	No dose modification + G-CSF

and Platelets > 100 000/mm^3		
Platelets < 100 000/mm^3 Whatever the number of ANC	J21*	Reduce by 1 dose level

* or until 28th day as needed (maximum)
Modalities of Reintroduction of treatment : ANC ≥ 1500/mm^3 **and** Platelets ≥ 100 000/mm^3
If the Platelets and/or ANC values are not correct at D28, the patient will discontinue permanently the study treatment.

At the time of Nadir
In the case of a grade 4 neutropenia, whatever the duration or complication i.e by an infection or fever > 38°5, the G-CSF will be administered at the next course of treatment. If the same toxicity continues with G-CSF then the irinotecan dose will be reduced at the dose immediately inferior. If there is a third occurrence of this toxicity, the patient will permanently discontinue the study treatment.

Table 5: Action and dose modification during the administration of Regorafenib in case of hematological toxicity

Hematological toxicity (Modification dose/delay for Regorafenib)		
Grade	Treatment delay	Dose modification
Grade 0-2	No delay in Regorafenib treatment	No modification dose
Grade 3	No delay in Regorafenib treatment	Reduce by 1 dose level[bc]
Grade 4	Interrupt Regorafenib until hematologic toxicity resolves to Grade ≤ 2[a]	Reduce by 1 dose level[bc]

a If no recovery within 30 days, the treatment will be permanently discontinued.
b If more than 2 dose reductions are necessary, the treatment will be permanently discontinued.
c Cf table a.

Table 6: Action and dose modification during the administration of Regorafenib in case of non-hematologic toxicity

Non-hematological toxicity (dose modification/delay for Regorafenib) (except hand-foot skin reaction, hypertension, liver function test abnormalities and diarrhea)[a]		
Grade	Treatment delay	Dose modification
Grade 0-2	No delay in Regorafenib treatment	No dose modification
Grade 3	Interrupt Regorafenib until non hematologic toxicity resolves to Grade ≤ 2[b]	Reduce by 1 dose level[cd]
Grade 4	Discontinue treatment permanently	Discontinue treatment permanently

a In the absence of nausea/vomiting prophylaxis and diarrhea not treated.

b If more than 2 dose reductions are necessary, the treatment will be permanently discontinued.

c If no recovery within 30 days, the treatment will be permanently discontinued.

d Cf table a.

Table 7: Delay and dose modification during the administration of Regorafenib in case of hand-foot skin reaction

Skin Toxicity Grade	Occurrence	Suggested Dose Modification
Grade 1: Numbness, dysesthesia, paraesthesia, tingling, painless swelling, erythema or discomfort of the hands or feet which does not disrupt the patient's normal activities	Any	Maintain dose level and institute immediately supportive measures for symptomatic relief

Grade 2: Painful erythema and swelling of the hands or feet and/or discomfort which affects the patient's normal activities	1st occurrence	Decreasing dose by one dose level[a] and institute immediately supportive measures. If no improvement , interrupt therapy for a minimum of 7 days, until toxicity resolves to Grade 0-1[b.]
	No improvement within 7 days or 2nd occurrence	Interrupt Regorafenib until toxicity resolves to Grade 0-1. When resuming treatment, treat at reduced dose level[ab]
	3rd occurrence	Interrupt Regorafenib until toxicity resolves to Grade 0-1. When resuming treatment, decrease dose by one additional dose level[a b c]
	4th occurrence	Discontinue treatment permanently
Grade 3: Moist desquamation, ulceration, blistering or severe pain of the hands or feet, or severe discomfort that causes the patient to be unable to work or perform activities of daily living.	1st occurrence	Institute supportive measures immediately. Interrupt therapy for a minimum of 7 days until toxicity resolves to Grade 0-1. When resuming treatment, decrease dose by one dose level[ab]
	2nd occurrence	Institute supportive measures immediately. Interrupt therapy for a minimum of 7 days until toxicity resolves to Grade 0-1. When resuming treatment, decrease dose by one dose level[a b c]
	3rd occurrence	Discontinue treatment permanently
a Cf table a		
b If toxicity returns to Grade 0-1 after dose reduction, dose re-escalation is permitted at the discretion of the investigator		
c Subjects requiring > 2 dose reductions should discontinue treatment		

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 (114)

Topical corticosteroids should be considered for subjects with Grade 2 or 3 hand-foot skin reaction (114). 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 8: Management of treatment-emergent hypertension

NCI-CTCAE V. 5.0 grade	Definition	Antihypertensive therapy	Regorafenib dosing
1	Prehypertension (systolic BP 120 - 139 mmHg or diastolic BP 80 - 89 mmHg)	None	Continue regorafenib Consider increased BP monitoring
2	Systolic BP 140 - 159 mmHg or diastolic BP 90 - 99 mmHg, OR Symptomatic increase by > 20 mmHg (diastolic) if previously within normal limits	Treat with the aim to achieve diastolic BP ≤ 90 mmHg: - If BP previously within normal limits, start antihypertensive monotherapy. - If subject already on antihypertensive medication, titrate up the dose.	Continue regorafenib If symptomatic, hold regorafenib until symptoms resolve AND diastolic BP ≤ 90 mmHg.[a] When regorafenib is restarted, continue at the same dose level.

3	Systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg OR More than one drug or more intensive therapy than previously used indicated	Treat with the aim to achieve diastolic BP ≤ 90 mmHg: - Start antihypertensive medication AND/OR - Increase current	Hold regorafenib until diastolic BP ≤ 90 mm Hg, and if symptomatic, until symptoms resolve.[a] When regorafenib is restarted, continue at the same dose level. If BP is not controlled with the addition of new or more intensive therapy,
		antihypertensive medication AND/OR - Add additional antihypertensive medications.	reduce by 1 dose level.[bd] If Grade 3 hypertension recurs despite dose reduction and antihypertensive therapy, reduce another dose level.[cd]
4	Life-threatening consequences (e.g, malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis		Discontinue therapy

BP = blood pressure; NCI-CTCAE=National Cancer Institute-common terminology criteria for adverse events
a Subjects requiring a delay of study treatment > 4 weeks should go off regorafenib.
b If BP remains controlled for at least one full cycle, dose re-escalation is permitted at the investigator's discretion.
c Subjects requiring > 2 dose level reductions (< 80 mg reduction) should go off regorafenib therapy.
d Cf table a.

Blood Pressure should be monitored weekly for the first 6 weeks of treatment. The 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 11]). Subjects' 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.

Table 9: Drug-related liver function test abnormalities

Elevations of alanine aminotransférase (ALT) and/or aspartate aminotransférase (AST)	Occurence	Management
≤ 5 times upper limit of normal (ULN) (Grade 2)	Any occurence	Continue treatment by Regorafenib. Control liver function every week until ALT and AST values return to < 3 times ULN (grade 1) orbaseline .
> 5 times ULN AND ≤ 20 times ULN (Grade 3)	1st occurence	Interrupt Regorafenib. Control ALT and AST values every week until they return to < 3 times ULN or baseline. Resuming treatment: if the potential benefit outweighs the risk of hepatic toxicity, reintroduce Regorafenib and reduce the dose of one tablet (40 mg) and control liver function every week for at least 4 weeks.
	2nd	Discontinue regorafenib

	occurence	permanently
> 20 times ULN (Grade 4)	Any occurence	Discontinue regorafenib permanently
> 3 times ULN (Grade 2 or higher) with concomitant elevation of bilirubin > 2 times ULN	Any occurence	Discontinue regorafenib permanently Control liver function every week until resolution or return to baseline

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

Other toxicities

The other toxicities will have to manage symptomatically, if possible. For any toxicity grade ≥ 2 at D15 except alopecia and anemia, the irinotecan will be delayed up to two weeks and the toxicity will have to be grade ≤ 1 to perform the course.

ARM B: STIVARGA® (REGORAFENIB)

Dosage changes should be made in 40 mg increments (1 tablet). The recommended daily dose of Regorafenib is 160 mg.

Dose reductions of Stivarga ®
1st reduction : 120 mg
2nd reduction : 80 mg

Table b

Table 10: Dose modification/Delay for toxicities related to study drug (except hand-foot Skin reaction and hypertension)[a]

NCI-CTC V5.0	Dose Interruption	Dose Modification	Dose for Subsequent Cycles
Grade 0-2	Treat on time	No change	No change
Grade 3	Delay until <	Reduce 1 dose level[c]	If toxicity remains < Grade 2,

	Grade 2[b]		dose re-escalation can be considered at the discretion of the treating investigator. If dose is re-escalated and toxicity (Grade 3) recurs, institute permanent dose reduction.
Grade 4	Delay until < Grade 2[b]	Reduce by 1 dose level[c]. Permanent discontinuation can be considered at treating investigator's discretion.	
a Excludes alopecia, non-refractory nausea/vomiting, non-refractory hypersensitivity and asymptomatic laboratory abnormalities. b If no recovery after a 4 week delay, treatment will be permanently discontinued. c Cf table b.			

Table 11: Dose modifications for hand-foot skin reaction

Skin Toxicity Grade	Occurrence	Suggested Dose Modification
Grade 1: Numbness, dysesthesia, paraesthesia, tingling, painless swelling, erythema or discomfort of the hands or feet which does not disrupt the patient's normal activities	Any	Maintain dose level and institute immediately supportive measures for symptomatic relief
Grade 2: Painful erythema and swelling of the hands or feet and/or discomfort which affects the patient's	1st occurrence	Decreasing dose by one dose level and institute immediately supportive measures. If no improvement , interrupt therapy for a minimum of 7 days, until toxicity resolves to Grade 0-1[b]

normal activities	No improvement within 7 days or 2nd occurrence	Interrupt Regorafenib until toxicity resolves to Grade 0-1. When resuming treatment, treat at reduced dose level[ab]
	3rd occurrence	Interrupt Regorafenib until toxicity resolves to Grade 0-1. When resuming treatment, decrease dose by one additional dose level[a b c]
	4th occurrence	Discontinue treatment permanently
Grade 3: Moist desquamation, ulceration, blistering or severe pain of the hands or feet, or severe discomfort that causes the patient to be unable to work or perform activities of daily living.	1st occurrence	Institute supportive measures immediately. Interrupt therapy for a minimum of 7 days until toxicity resolves to Grade 0-1. When resuming treatment, decrease dose by one dose level[ab]
	2nd occurrence	Institute supportive measures immediately. Interrupt therapy for a minimum of 7 days until toxicity resolves to Grade 0-1. When resuming treatment, decrease dose by one additional dose level[a b c]
	3rd occurrence	Discontinue treatment permanently
a Cf table b		
b If toxicity returns to Grade 0-1 after dose reduction, dose re-escalation is permitted at the discretion of the investigator		
c Subjects requiring > 2 dose reductions should discontinue treatment		

If no recovery after a 4 week delay, treatment will be discontinued permanently.

For subjects who require a dose reduction for Grade 2 or 3 rash or hand-foot skin reaction (HFSR), the dose of study drug may be increased to the starting dose after one full cycle of therapy has been Administered with the reduced dose without the appearance of rash or HFSR > Grade 1.

The following measurements should be considered for prevention and treatment of hand-foot skin reaction:

Termination of Stivarga® :

-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

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
- Udderly Smooth
- Gold Bond
- 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 (114)

Topical corticosteroids like clobetasol 0.05% should be considered for subjects with Grade 2 or 3 hand-foot skin reaction (114). 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: Management of treatment-emergent hypertension

NCI-CTCAE V5.0 grade	Definition	Antihypertensive therapy	Regorafenib dosing
1	Prehypertension (systolic BP 120 - 139 mmHg or diastolic BP 80 - 89 mmHg)	None	Continue regorafenib. Consider increased BP monitoring.
2	Systolic BP 140 - 159 mmHg or diastolic BP 90 - 99 mmHg, OR Symptomatic increase by > 20 mmHg (diastolic) if previously within normal limits	Treat with the aim to achieve diastolic BP ≤ 90 mmHg: - If BP previously within normal limits, start antihypertensive monotherapy. - If subject already on antihypertensive medication, titrate up the dose.	Continue regorafenib. If symptomatic, hold regorafenib until symptoms resolve AND diastolic BP ≤ 90 mmHg.[a] When regorafenib is restarted, continue at the same dose level.

3	Systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg OR More than one drug or more intensive therapy than previously used indicated	Treat with the aim to achieve diastolic BP ≤ 90 mmHg: - Start antihypertensive medication AND/OR - Increase current antihypertensive medication AND/OR - Add additional Antihypertensive medications.	Hold regorafenib until diastolic BP ≤ 90 mm Hg, and if symptomatic, until symptoms resolve.[a] When regorafenib is restarted, continue at the same dose level. If BP is not controlled with the addition of new or more intensive therapy, reduce by 1 dose level.[be] If Grade 3 hypertension recurs despite dose reduction and antihypertensive therapy, reduce another dose level. [ce]
4	Life-threatening consequences (e.g, malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis		Discontinue therapy

BP = blood pressure; NCI-CTCAE=National Cancer Institute-common terminology criteria for adverse events
a Subjects requiring a delay of study treatment > 4 weeks should go off regorafenib.
b If BP remains controlled for at least one full cycle, dose re-escalation is permitted at the investigator's discretion.
c Subjects requiring > 2 dose level reductions (< 80 mg reduction) should go off regorafenib therapy.
d Cf table a.

Blood Pressure should be monitored weekly for the first 6 weeks of treatment. The 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]). Subjects' 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.

Table 13 : Drug-related liver dysfunction

Elevations of alanine aminotransférase (ALT) and/or aspartate aminotransférase (AST)	Occurence	Management
≤ 5 times upper limit of normal (ULN) (Grade 2)	Any occurence	Continue treatment by Regorafenib. Control liver function every week until ALT and AST values resolve to < 3 times ULN (grade 1) or to their initial value.
> 5 times ULN AND ≤ 20 times ULN (Grade 3)	1st occurence	Interrupt Regorafenib. Control ALT and AST values every week until they resolve to < 3 times ULN or their initial value. Resuming treatment: if the benefice is superior to the risk of hepatic toxicity, reintroduce Regorafenib and reduce the dose of one tablet (40 mg) and control liver function every week for at least 4 weeks.
	2nd occurence	Discontinue regorafenib permanently

> 20 times ULN (Grade 4)	Any occurence	Discontinue regorafenib permanently
> 3 times ULN (Grade 2 or beyond) with concomitant elevation of bilirubin > 2 times ULN	Any occurence	Discontinue regorafenib permanently Interrupt Regorafenib until toxicity resolves to Grade 0-1. Control liver function every week until ALT and AST values resolve to < 3 times ULN (grade 1) or to their initial value.

6.4 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.

6.4.1 Other treatments/procedures

Permitted 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.

- 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 permitted.

- CYP isoform-selective substrates
  In vitro data indicate that regorafenib is a competitive inhibitor of the cytochromes CYP2C8 (K_i value of 0.6 micromolar), CYP2C9 (K_i value of 4.7 micromolar), CYP2B6 (K_i 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 (K_i value of 11.1 micromolar) and CYP2C19 (K_i 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.

- Clinical data indicate that regorafenib has no effect on digoxin pharmacokinetics, therefore can be given concomitantly with p-glycoprotein substrates, such as digoxin, without a clinically meaningful drug interaction

6.5 Non permitted treatment

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 UGT1A1 and 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.

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.

-Systemic anticancer therapy including cytotoxic therapy, signal transduction inhibitors, immunotherapy, hormonal therapy and experimental or approved therapies during this trial or within 30 days before starting to receive study medication.

-Bone marrow transplant or stem cell rescue.

-Prior radiation and concomitant palliative radiation therapy is allowed if the target lesion(s) are not included within the radiation field and no more than 10% of the bone marrow is irradiated.

-Use of biologic response modifiers, such as granulocyte colony stimulating factor (GCSF), within 3 weeks of study entry.

-Herbal medicine and grapefruit juice

-Yellow fever vaccine: Risk of fatal generalized vaccine disease

-Live attenuated vaccines: Risk of generalized vaccine disease, possibly fatal. Concomitant administration during treatment with irinotecan and for 3 months after discontinuation of

chemotherapy is contraindicated. Killed or inactivated vaccines can be administered, however the response to these vaccines can be decreased.

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

-Neuromuscular blocking agents: the interaction between irinotecan and neuromuscular blocking agents cannot be ruled out. Due to the anticholinesterase activity of irinotecan, drugs with anticholinesterase activity can prolong the neuromuscular blocking effects of suxamethonium and the neuromuscular blockade of non-depolarizing agents can be antagonized.

-Antivitamin K such as warfarin, phencoumarone etc.

7. Ancillary Studies

7.1. IMMUNOHISTOCHEMISTRY STUDY

The expression of cyclin D1 protein will be sought by immunohistochemistry on tissue sections of paraffin-embedded specimens.
We will investigate any association between protein expression and response to treatment.

In addition, depending on the progress of knowledge at the time of the study is completed, other biomarkers predictive of response to treatment can be explored by IHC on the same tumor blocks.
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
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

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

8. Discontinuation criteria/Subject withdrawal/end of study

8.1. 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 reported as a serious adverse event.
- 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).

8.2. 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.

8.3. END OF STUDY

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

9. Statistical considerations

9.1 Sample size

The main objective is the comparison of overall survival in the regorafenib and REGIRI combination (Regorafenib + Irinotecan) arms in mCRC patients harboring Cyclin D1 A/A genotype.

The aim is to increase the median overall survival from an estimated baseline of 7 to 15 months corresponding to 1-year OS of 30% to 57%, respectively with a HR=0.47. A total of **55 events are required** to detect this difference if it is true with 80% power and using a 2–sided log-rank test at the 5% level of significance.

A total number of required patients is 68 without drop-out.

Considering 15% additional patients lost to follow-up on estimated patients number, the sample size is 78 patients (2*39) to observe the required number of events.

Because the A/A CCND1 genotype is present in 25% of patients with metastatic colorectal cancer, 312 patients will need to be screened.

No interim analysis was planned.

9.2 Study populations

Different population of patients may be defined for the analysis:

- Per-Protocol (PP) population = all patients in the ITT population without major protocol deviations that impact assessment of efficacy.
  The PP Analysis will be used to perform sensitivity analysis for the primary endpoint.
- Intent To Treat (ITT) population = all randomized patients analyzed in their randomized arm.
- Eligible population: all patients without major inclusion criteria (CI n°1, n°3, n°4, n°5, n°8) or non-inclusion violation (n°2, n°3, n°7, n°8).
- Safety population = all treated patients who received at least one dose of treatment
- Modified Intent To Treat (ITT) population = eligible population in their randomized arm.

9.3 Statistical methods

A Statistical Analysis Plan (SAP) will be written before the database is locked. Populations are defined in section 9.2.

All statistical analyses will be performed on ITT population.

Safety analysis will be performed on safety population

Sensitivity analysis will be performed on Modified Intent To Treat (ITT) population for primary endpoint.

Descriptive analyses (in each arm) will be performed using median and range for continuous parameters, frequency and percentage for categorical variables.

Baseline characteristics of randomized patients in each arm will be compared by Kruskal-Wallis tests or Wilcoxon for continuous variables, or chi 2 or Fisher exact test for categorical variables

The primary efficacy endpoint of OS will be compared using a two-sided stratified log-rank test. The analysis will be stratified by RAS. Kaplan-Meier (KM) estimates for OS and KM survival curves will also be presented for each group. The KM estimates at time points such as 6 months and 12 months, together with corresponding 95% confidence intervals as well as the differences of these estimates will be calculated between the REGIRI and Regorafenib arms.

With regard to the secondary efficacy endpoint PFS, the 2 treatment groups will be compared using a log-rank test stratified by RAS. Hazard ratios and 95% CI will be provided. KM estimates and KM curves will also be presented for each treatment arm. The KM estimates at time points such as 3 months and 6 months, together with corresponding 95%

confidence intervals as well as the differences of these estimates between the REGIRI arm and the Regorafenib arm will also be calculated.
Objective response rate as well as DCR will be compared between treatment groups using the Cochran-Mantel-Haenszel test. Estimates and 95% confidence intervals will be computed for each treatment arm. The differences in ORR and DCR between the REGIRI and regorafenib arms and the corresponding 95% confidence intervals will also be calculated.
Summary statistics will be displayed for all best response categories: CR, PR and SD.
Descriptive summary tables will be presented for all safety parameters by each treatment group. All AEs, as well as drug-related AEs and SAEs will be summarized by NCI-CTCAE version 5 (appendix 9) categories and worst grade.
PRO data as measured by the EORTC QLQ-C30 (appendix 2) will be analyzed to assess differences in health-related quality of life (HRQOL) values between treatment arms.

HRQOL scores were described for each assessment and compared either between treatment arms (rank sum test). The missing data pattern was studied by the comparison of the baseline characteristics between patients who either completed baseline HRQOL questionnaires or not. The compliance of the patients was also described using fill rate at each visit and for each questionnaire.

Longitudinal analyses were performed using two approaches:
(1) A LMM analysed the evolution of scores through time and combined fixed effects [Cnaan A, Laird NM, Slasor P. Using the general linear mixed model to analyse unbalanced repeated measures and longitudinal data. Stat Med 1997;16:2349-80.+ Fairclough DL. Design and analysis of quality of life studies in clinical trials. 2002.] for study group, time factors, treatment-by-time interaction effects and random effects allowing specific correlations between observations for a particular patient. This mode l assumed no difference between the treatment arms at baseline.
(2) A time to event approach considered the definitive deterioration of a HRQOL score as an event. Osoba et al. [Osoba D, Rodrigues G, Myles J, Zee B, Pater J.

Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol 1998;16:139-44.] showed that a mean change of 5-10 pts, 10-20 pts and >20 pts in a QLQC30 score corresponds to a “small”, “moderate” and “large” change in HRQOL. This definition was applied to indicate the clinical relevance of any differences. TUDD was defined as the time from randomisation to the first score deterioration with a 10-point minimal

clinically important difference (MCID) as compared with the baseline score, with no further improvement superior to 10 points as compared with baseline or with no available HRQoL score [Anota A, Hamidou Z, Paget-Bailly S, Chibaudel B, Bascoul-Mollevi C, Auquier P, et al. Time to health-related quality of life score deterioration as a modality of longitudinal analysis for health-related quality of life studies in oncology: do we need RECIST for quality of life to achieve standardization? Qual Life Res 2015;24:5-18. + Bonnetain F, Dahan L, Maillard E, Ychou M, Mitry E, Hammel P, et al. Time until definitive quality of life score deterioration as a means of longitudinal analysis for treatment trials in patients with metastatic pancreatic adenocarcinoma. Eur J Cancer e Oxf Engl 1990 2010;46:2753-62. + Hamidou Z, Dabakuyo TS, Mercier M, Fraisse J, Causeret S, Tixier H, et al. Time to deterioration in quality of life score as a modality of longitudinal analysis in patients with breast cancer. Oncologist 2011;16:1458-68.].

Sensitivity analyses were also performed. A survival analysis was also performed to determine baseline prognostic factors for PFS and OS. A Cox proportional hazard model was performed following the method published in EORTC meta-analyses [Quinten C, Martinelli F, Coens C, Sprangers MAG, Ringash J,Gotay C, et al. A global analysis of multitrial data investigating quality of life and symptoms as prognostic factors for survival in different tumor sites. Cancer 2014;120:302-11., + Quinten C, Coens C, Mauer M, Comte S, Sprangers M, Cleeland C, et al. Baseline quality of life as a prognostic indicator of survival: a meta-analysis of individual patient data from EORTC clinical trials. Lancet Oncol 2009;10:865-71.]. Baseline QLQ-C30 scores were entered as continuous variables. Hazard ratios were calculated for every 10-point difference to take into account a 10-point MCID [Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol 1998;16:139-44. + Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. Control Clin Trials 1989;10:407-15.].

All statistical analyses will be performed with the Stata v13 software.

10. Vigilance and safety control

10.1 Adverse Events

10.1.1 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.

10.1.2 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.

10.1.3 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.

10.2 Serious Adverse Events, New Event and Urgent Safety Measure (USM)

10.2.1 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 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 leading to a reassessment of the benefits / risks balance of the research or product of the research, to changes in the use of the product or in the conduct on documents related to the research, or to discontinuation, arrest or modification of the research protocol or that of similar research.

For trials assessing first administration or use of a product in persons with no specific disease (healthy volunteer): any serious adverse event.

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).

10.2.2 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 for Regorafenib alone arm and for Irinotecan
- The latest version of the investigator's brochure (IB) for Regorafenib in the REGIRI arm.

10.2.3 Pregnancy

According to the regulatory recommendations with respect to potential genotoxicity and teratogenicity (CFTG 21/09/2020, version 1.1) the durations of contraceptives for women of childbearing potential (WOCBP) and men to ensure effective contraception during treatment with regorafenib are respectively 7 months and 4 months in men sexually active with women of childbearing potentiel after last dose of regorafenib.

For Irinotecan, the durations of contraceptives for women of childbearing potential (WOCBP) and men are respectively 6 months and 3 months in men sexually active with women .

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.

10.2.4 SAE, New Event, Urgent Safety Measure, and Pregnancy Notification Procedure

10.2.4.1 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 the 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

Mail:

Notification-EIG-DRCI@icm.unicancer.fr

For other safety information:

Pharmacovigilance-icm105@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 sent 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 Vigilance 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.

10.2.4.2 New Event / Urgent Safety Measure / Notification Procedure

Any New Event, and 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

10.2.4.3 Pregnancy Notification Procedure

Pregnancies and suspected pregnancies occurring during the study period (from the signature of the informed consent form until up to 2 months after the withdrawal of Regorafenib, and 3 months after the withdrawal of Irinotecan for female patients and 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.

10.2.4.4 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

10.2.5 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 safety event 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
Other SUSARs	Within 15 days after the sponsor has taken notice of this event	Within maximum 8 days after the sponsor has taken notice
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 delay)	Request for substantial modification Within maximum 15 days after the sponsor has taken notice

10.3 Independent Safety Committee (ISC)

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

During a trial the ISC can 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 scheduled time point will be after the enrolment of the first twenty patients (arm A) and will be about the safety of the first two months of treatment.

The Sponsor could ask the ISC for an ad hoc advice throughout the study concerning safety and inclusions.

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

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.

11. Quality assurance and control

11.1. 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
Data center UNICANCER
From Monday to Friday 9am-5pm
Email: support.ecrf**base**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.

11.2 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.

11.3 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.

12. Administrative, ethical and regulatory aspects

12.1. 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.

12.2. 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.

12.3. 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, 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. 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.

European Regulation 2016/619 on the protection of individuals with regard to the processing of personal data and on the free movement of such data, known as the "DGPS" (General Regulation on Data Protection) will be applicable on May 25, 2018.

12.4. 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.

12.5. 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.

12.6. 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.

12.7. 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.

13. Financing and Insurance

13.1. Financing of Research

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

13.2. Insurance

Insurance has been subscribed by the sponsor (ICM) to RELYENS (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.

14. Publication policy and communication

14.1. 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 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.
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It may appear in the acknowledgements at the end of the article:
-patients and their families;
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-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.

14.2. Data sharing statements

14.3.

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 and where? 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.

15. References

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