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A Randomized, phase II study comparing the sequences of Regorafenib and Trifluridine/Tipiracil, after failure of standard therapies in patients with metastatic colorectal cancer

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Background

Colorectal Cancer is the third most common cancer, with an estimated 1.8 million new cases and 880.000 deaths per year (Bray, Ferlay et al. 2018). Median Overall Survival of Metastatic Colorectal Cancer (mCRC) is about 30 months. In the last decade, survival of mCRC patients has improved due to better treatment and disease management.

Currently, first-line chemotherapy for mCRC consists of a fluoropyrimidine-based chemotherapy combined with oxaliplatin and/or irinotecan, associated with an anti-VEGF inhibitor or an anti-EGFR inhibitor.

Once all the above-mentioned treatment options have been used, patients are eligible for either Regorafenib or Trifluridine-Tipiracil treatment. No study compared the two treatments in this setting, except the REGOTAS retrospective study (Moriwaki et al, 2018) that found no difference in Overall Survival between the two treatments. Moreover, no randomized trial has investigated **the sequencing of Regorafenib and Trifluridine-Tipiracil.**

We have designed the SOREGATT study to evaluate which sequence will be better in this setting. We aim to determine the **optimal treatment strategy,** which could **improve the current clinical practice** for mCRC patients.

Objectives

Primary objective :

To compare the feasibility of the treatment sequences :

- **A : Regorafenib then Trifluridine/Tipiracil**
- **B : Trifluridine/Tipiracil then Regorafenib**

Secondary objectives :

- **EFFICACY**:
  - Overall Survival **(OS)**
  - Progression-Free Survival **(PFS)** *for both sequences of treatment in each arm*
  - Disease Control Rate **(DCR)** *in each study arm*
  - Objective Response Rate **(ORR)** *in each study arm*
  - Time-to-Treatment Failure **(TTF)** *for both sequences of treatment in each arm*
  - Time to deterioration (ECOG PS ≥2) *for both sequences of treatment in each arm*
- **QUALITY OF LIFE:** Patient-Reported Outcome EORTC QLQ-C30 v3.0
- **SAFETY :** Tolerance of the treatment sequences

Participating sites

Study Status

Study timelines

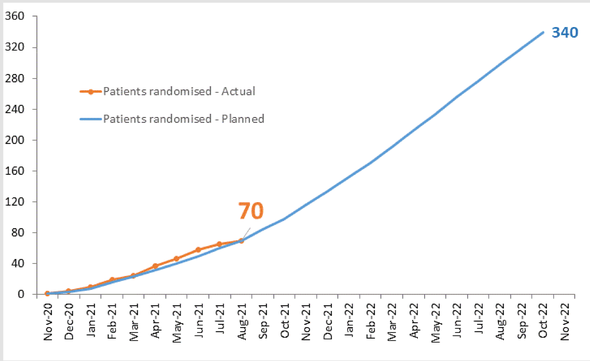
First patient included : November 2020
Expected Completion of recruitment : November 2022
Primary endpoint analysis expected in **November 2023**

International involvement—Regulatory phase

- Belgium : Approval was obtained from the Health Authority, pending from the Ethics Committee. Sites opening planned in Q3 2021
- Italy : Submission package in progress. Sites opening planned in Q1 2022.

Recruitment status

As of August 30th 2021, **70** patients were randomized.



Translational research : predictive biomarkers measurement

- Tumour samples will be collected at baseline.
- Blood samples will be collected at baseline and during treatment phase.

Funding

Study sponsored by Bayer

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Study Population

Patients aged ≥18 years old with mCRC, after failure of fluoropyrimidine-based chemotherapy, as well as VEGF and EGFR inhibitors *in patients eligible for these treatments.*

Main Inclusion Criteria

- Metastatic adenocarcinoma of the colon or rectum histologically or cytologically confirmed
- Patients must have progressed following exposure of all the following agents : one fluoropyrimidine-based chemotherapy combined with oxaliplatin and/or irinotecan (including FOLFOX, FOLFIRI or FOLFOXIRI), as well as EGFR and/or VEGF inhibitors *(in patients eligible for these treatments)*
- ECOG Performance Status ≤1
- Adequate bone marrow, liver and renal functions

Main Exclusion Criteria

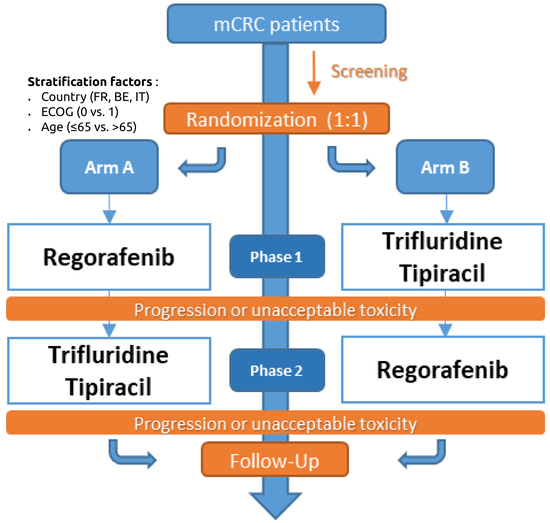
- Symptomatic brain or meningeal metastasis, unless definitive therapy occured ≥ 6 months ago and with a confirmation of tumoral control within 4 weeks of starting study treatment
- Previous or concurrent cancer that is distinct in primary site or histology from CRC within 5 years prior to inclusion, *except for curatively treated in situ cervical cancer, non melanoma skin cancer, and supperficial bladder tumors: staged Ta, Tis and T1*
- Prior treatment with study treatments (or any other tyrosine kinase inhibitor)
- Active cardiac disease
- Bowel malabsorption, occlusive syndrome, presence of gastro-intestinal fistula or perforation

Wash-out period *(previous treatments)*

Chemotherapy : 3 weeks, Radiotherapy : 4 weeks (if palliative : 2 weeks), Other experimental drug : 30 days

Study design

Multicenter, international, comparative, open-label, phase II study conducted in 2 parallel groups



Treatments

- Regorafenib : 160 mg per day for 3 weeks, followed by 1 week off
  Cycle 1 only : 80 mg per day at week 1, 120 mg per day at week 2, 160 mg per day at week 3, followed by 1 week off (ReDOS)
- Trifluridine/Tipiracil : 35 mg/m² administered orally twice daily, on Days 1 to 5 and 8 to 12 of each 4-week cycle

Statistical considerations

Primary endpoint analysis : Feasibility of the 2 sequences assessed as the percentage of patients able to receive at least 2 cycles of both treatments, which corresponds to the 1st tumour evaluation.

If a patient does not receive the 2nd treatment, it will be considered as a failure.

Required number of patients : 340 patients are necessary to demonstrate a difference of 15% between the two arms (Chi-square test, bilateral type I error 5%, power 80%).

Based on the data of Moriwaki et al, 2018 : 65% of the subjects receiving Regorafenib were able to receive further treatment, versus 50% of the subjects receiving Trifluridine-Tipiracil.

Populations :

- Intention-to-Treat analysis will be conducted for all efficacy endpoints
- Safety populations will include all patients who have received at least one dose of either drug

Acknowledgment

We thank the patients and their families for participating in the study.
We also value the involvement of all the participating centers.

For additional information, please contact the study coordinator :
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Prof. Ducreux, as first author, declares that there is no conflict of interest.