# A prospective, observational trial to assess the safety and efficacy of regorafenib in patients with metastatic colorectal cancer (mCRC) in routine clinical practice (CORRELATE)

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## BACKGROUND

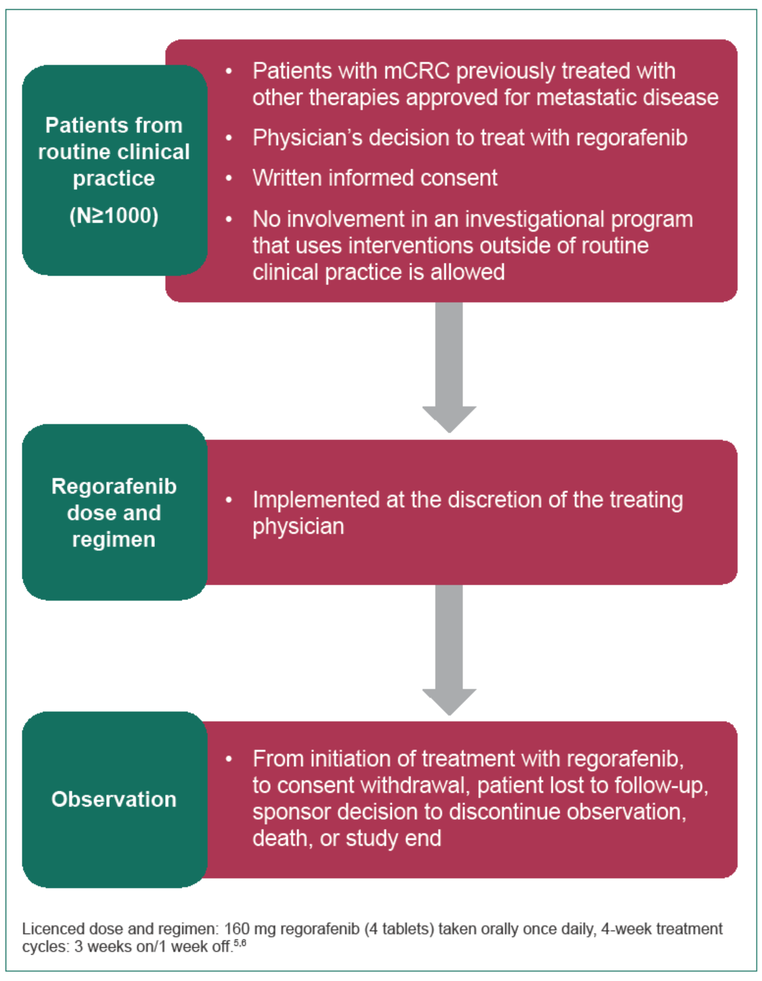
- The current standard of care for unresectable mCRC includes fluoropyrimidine-based chemotherapy with or without bevacizumab; epidermal growth factor receptor (EGFR) inhibitors such as cetuximab and panitumumab are recommended for patients with *KRAS* wild-type tumors[1]
  - Few options are available for patients following disease progression with standard therapies
- Regorafenib is an oral multikinase inhibitor that blocks the activity of multiple protein kinases involved in oncogenesis, tumor angiogenesis, and the tumor microenvironment[2]
- In the randomized, double-blind, international phase III CORRECT trial and the phase III CONCUR trial in Asian patients, regorafenib significantly improved overall survival (OS) and progression-free survival (PFS) versus placebo in patients with mCRC who had progressed on standard therapies[3,4]
  - CORRECT: OS, hazard ratio (HR) 0.77, 95% CI 0.64–0.94; one-sided P=0.0052[3]
  - CONCUR: OS, HR 0.55, 95% CI 0.40–0.77; one-sided P=0.00016[4]
  - Adverse events (AEs) were similar in both trials, with most frequent AEs including hand–foot skin reaction, fatigue, diarrhea, HTN, and elevated liver enzymes
- CORRELATE aims to characterize the safety and efficacy of regorafenib for the treatment of mCRC in an unselected real-world patient population treated in routine clinical practice

## METHODS

### Study design

- CORRELATE (NCT02042144) is a prospective, observational, multicenter trial conducted in routine clinical practice (Figure 1)

***Figure 1:** CORRELATE study design*




Licenced dose and regimen: 160 mg regorafenib (4 tablets) taken orally once daily, 4-week treatment cycles: 3 weeks on/1 week off.[5,6]

- Dose modifications are recommended for the management of drug-related AEs (Tables 1–2)[3,7]

***Table 1:** Dose modifications and delays for study drug-related toxicities other than HFSR, liver function test abnormalities, and hypertension* as recommended in the CORRECT study protocol[3]*

| NCI-CTCAE grade | Dose interruption | Dose modification | Dose for subsequent cycles |
|---|---|---|---|
| Grade ≤2 | Treat on time | No change | No change |
| Grade 3 | Delay until grade <2† | Reduce by 1 dose level | If toxicity remains at grade <2, dose re-escalation can be considered<br>If dose is re-escalated and grade ≥3 toxicity recurs, implement permanent dose reduction |
| Grade 4 | Delay until grade <2† | Reduce by 1 dose level. Permanent discontinuation can be considered | |

*Excludes alopecia, non-refractory hypersensitivity or nausea/vomiting, and asymptomatic laboratory abnormalities.

†If no recovery after a 4-week delay, regorafenib should be discontinued permanently.

HFSR, hand–foot skin reaction; NCI-CTCAE, National Cancer Institute Common Toxicity Criteria for Adverse Events.

***Table 2:** Dose modifications for HFSR as recommended in the CORRECT study protocol[3]*

| Skin toxicity grade | Occurrence* | Suggested dose reduction/ interruption* |
|---|---|---|
| Grade 1: Numbness, dysesthesia, paresthesia, tingling, painless swelling, erythema, or discomfort of the hands or feet that does not disrupt the patient's normal activities | Any | Maintain dose level and immediately implement supportive measures for symptomatic relief |
| Grade 2: Painful erythema and swelling of the hands or feet and/ or discomfort that affects the patient's normal activities | First occurrence | Consider decreasing dose by 1 dose level and immediately implement supportive measures. If no improvement, interrupt therapy for a minimum of 7 days, until toxicity resolves to grade ≤1† |
| | No improvement within 7 days or second occurrence | Interrupt therapy until toxicity resolves to grade ≤1. When resuming treatment, treat at reduced dose level† |
| | Third occurrence | Interrupt therapy until toxicity resolves to grade ≤1. When resuming treatment, reduce dose by 1 additional dose level†‡ |
| | Fourth occurrence | Discontinue treatment |
| 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 | First occurrence | Immediately implement supportive measures. Interrupt therapy for a minimum of 7 days until toxicity resolves to grade ≤1. When resuming treatment, decrease dose by 1 dose level† |
| | Second occurrence | Immediately implement supportive measures. Interrupt therapy for a minimum of 7 days until toxicity resolves to grade ≤1. When resuming treatment, decrease dose by 1 additional dose level†‡ |
| | Third occurrence | Permanently discontinue treatment |

*A more conservative approach is acceptable, if medically indicated.

†If toxicity returns to grade ≤1 after dose reduction, dose re-escalation is permitted at the discretion of the physician.

‡Patients requiring >2 dose reductions (i.e., resulting in a <80 mg daily dose) should discontinue regorafenib therapy.

HFSR, hand–foot skin reaction.

### Study endpoints

- Primary endpoint:
  - Incidence of all treatment-emergent AEs (TEAEs) assessed using NCI-CTCAE v4.3
- Secondary endpoints:
  - OS (time from regorafenib initiation to death from any cause)
  - PFS (time from regorafenib initiation to radiologic or clinical disease progression or death, whichever comes first)
  - Disease control rate (complete response + partial response + stable disease [≥6 weeks duration])
  - Health-related quality of life, assessed using the EuroQol five-dimension questionnaire
  - Healthcare resource utilization (includes the proportion of patients hospitalized and the average length of hospitalization per admission)
- Data sources will include medical records, routine measurements, and patient-reported outcome questionnaires

### Analyses

- All patients receiving at least 1 dose of regorafenib will be included in the overall analysis
- Subgroup analyses stratified by prognostic/predictive factors collected at baseline may be explored
- Safety analyses will be performed for patients who progress by end of treatment cycle 1
- Hand–foot skin reaction rates will be calculated according to: (1) worst toxicity grade; (2) overall incidence; and (3) use of preventive measures
- One interim analysis will be performed after 500 patients have been observed for at least 3 months
- Final analysis will be performed once all patients have been enrolled and followed for 6 months after discontinuation of regorafenib, or until death, withdrawal of informed consent, or premature discontinuation, whichever occurs first
- Analyses are exploratory, not hypotheses testing

## ENROLLMENT

- CORRELATE will recruit at least 1000 patients from routine clinical practice settings across more than 25 countries in Latin America, Europe, and the Asia-Pacific region
- Recruitment is ongoing, with the first patient enrolled in April 2014
- As of June 2015, 98 patients have been enrolled in 7 countries
- The estimated primary completion date is September 2017

### References

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