

# Single-Agent Regorafenib in Metastatic Colorectal Cancer Patients with Any RAS or BRAF Mutation Previously Treated with FOLFOXIRI plus Bevacizumab (PREVIUM Trial)

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ON BEHALF OF THE SPANISH COOPERATIVE GROUP FOR THE TREATMENT OF DIGESTIVE TUMORS (TTD)

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## TRIAL INFORMATION

- **ClinicalTrials.gov Identifier:** NCT02175654
- **Sponsor(s):** Spanish Cooperative Group for the Treatment of Digestive Tumors (TTD)
- **Principal Investigator:** Pilar Garcia-Alfonso
- **IRB Approved:** Yes

## LESSONS LEARNED

- RAS- or BRAF-mutated metastatic colorectal cancers (mCRCs) progressing after first-line treatment have a poor prognosis.
- European and U.S. guidelines include the multikinase inhibitor regorafenib as a standard option for second-line therapy and beyond, based on the results of the randomized phase III CORRECT trial demonstrating improvement in survival.
- Although stopped prematurely for failing to accrue, the PREVIUM trial, the first prospective interventional study exploring regorafenib as second-line treatment for patients with mCRC bearing RAS or BRAF mutations, failed to demonstrate clinical activity in the population analyzed.

## ABSTRACT

**Background.** Patients with RAS- or BRAF-mutated (mut) metastatic colorectal cancer (mCRC) progressing on first-line bevacizumab plus 5-FU/irinotecan/oxaliplatin (FOLFOXIRI) have a poor prognosis. We aimed to assess the efficacy and safety of regorafenib in this population.

**Methods.** Regorafenib was administered daily for 3 weeks of each 4-week cycle until disease progression or other reason. The primary endpoint was 6-month progression-free survival (PFS).

**Results.** KRAS, NRAS, or BRAF was mutated in mCRC samples in 60%, 20%, and 13% of patients, respectively. Median time from initial diagnosis of metastases to the start of regorafenib and treatment duration was 13.8 months and 7 weeks, respectively. Reasons for discontinuation included disease progression (80%), investigator decision (13%), and adverse events (AEs; 7%). Seven

patients (47%) required dose reduction, mostly for asthenia (43%). The most common regorafenib-related grade 3 AEs were asthenia (33%), dysphonia (13%), and hypertension (13%) (Table 1). There were no grade 4 toxicities. No patient was progression-free at 6 months. Median PFS, time to progression (TTP), and overall survival (OS) were 2.2, 2.0, and 3.3 months, respectively.

**Conclusion.** Although stopped prematurely for failing to accrue, in the population analyzed, regorafenib failed to demonstrate clinical activity in KRAS- or BRAF-mutated mCRC with progression following first-line with FOLFOXIRI plus bevacizumab, although tolerability was acceptable. Our trial suggests that exploring regorafenib efficacy in an earlier line of therapy should not be undertaken without better population refinement. *The Oncologist* 2018;23:1271–e128

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## DISCUSSION

In relapsed wild-type-RAS mCRC, the current standard treatment is chemotherapy plus an anti-epidermal growth factor receptor (EGFR) antibody. For patients with mut-KRAS mCRC whose disease progresses following a first-line combination of FOLFOXIRI/bevacizumab, the choice of optimal systemic therapy has not yet been established. In this scenario, switching to a targeted agent such as a multikinase inhibitor is a valid and recommended approach, included in current European Society for Medical Oncology and National Comprehensive Cancer Network guidelines.

To our knowledge, this is the first prospective interventional study exploring regorafenib as second-line treatment for a mCRC population pretreated with the triplet FOLFOXIRI/bevacizumab, specifically enrolling patients with mut-KRAS or BRAF mCRC. Although enrollment was closed prematurely due to poor accrual, and definitive statements regarding the efficacy of regorafenib cannot be made, the study highlights several important lessons. The disappointing disease control rate compared with the pivotal phase III trial might be explained by the fact that patients included in our trial had some clinical and molecular high-risk and poor prognosis features. Noticeably, the median TTP on their first-line therapy was <14 months. Likewise, circulating tumor cell (CTC) counts were obtained. CTC counts have been validated as a prognostic marker in multiple clinical studies. In our study, 87% of patients had CTC counts >3 per 7.5 mL before their first-line treatment, this being considered a poor prognostic feature.

Lastly, our data on this selected population would suggest that KRAS- or BRAF-mutated mCRC is associated with inferior PFS and OS, reflecting that an interaction between baseline mutational status and treatment effect could not be excluded. Indeed, frequently debated is the influence of the mutated-EGFR status of patients included in regorafenib studies, particularly patients with tumors bearing mutations in RAS, which tend to be even less responsive to chemotherapy than tumors in a population with wild-type disease. Furthermore, mut-RAS mCRC exhibits a markedly higher cumulative incidence of lung, bone, and brain metastasis. In our study, 12 patients (80%) had a RAS mutation.

Our study results, in line with other similar trials, do not provide a signal that regorafenib would lead to improved clinical benefit for high-risk mCRC patients. As vascular endothelial growth factor (VEGF) axis inhibition underlies regorafenib activity, antiangiogenic properties and inflammation-related factors could play a role in modulating this lack of activity, as an inflammation-mediated cross-talk between endothelial cells and immune system effectors has been hypothesized to play a critical role in antiangiogenic therapy resistance. This systemic inflammatory status in advanced disease could reflect changes in tumor inflammatory microenvironment that would activate VEGF-independent angiogenesis.

With regard to its tolerability, regorafenib appears to be safe according to the observed toxicity profile. The frequency and severity of AEs was thus consistent with the known safety profile of regorafenib and other multikinase inhibitors.

## TRIAL INFORMATION

<b>Disease</b>	Colorectal cancer
<b>Stage of Disease/Treatment</b>	Metastatic/advanced
<b>Prior Therapy</b>	1 prior regimen
<b>Type of Study – 1</b>	Phase II
<b>Type of Study – 2</b>	Single arm
<b>Primary Endpoint</b>	Progression-free survival
<b>Secondary Endpoint</b>	Overall survival

### Additional Details of Endpoints or Study Design

Primary endpoint: 6-month PFS rate as per modified RECIST criteria. A sample size of 53 evaluable patients was necessary assuming a minimum of 30% patients achieving a PFS at 6 months, rejecting the null hypothesis of <15% PFS at 6 months, with an alpha error of 0.05 and statistical power of 80%.

Evidence-based medicine must be based on the best evidence, which may include negative studies. This research article, although stopped prematurely for failing to accrue, clearly documented a lack of efficacy of a targeted therapeutic agent in RAS- or BRAF-mutated mCRC progressing following first-line with FOLFOXIRI/bevacizumab.

### Investigator's Analysis

Level of activity did not meet planned endpoint

## DRUG INFORMATION

### Drug 1

<b>Generic/Working Name</b>	New drug
<b>Trade Name</b>	Stivarga
<b>Company Name</b>	Bayer AG
<b>Drug Type</b>	Small molecule
<b>Drug Class</b>	Angiogenesis
<b>Dose</b>	160 mg per flat dose
<b>Route</b>	p.o.

**Schedule of Administration**

Patients received regorafenib 160 mg once daily, for the first 21 days of each 28-day cycle until disease progression, unacceptable toxicity, withdrawal of the patient from the study, or death.

**PATIENT CHARACTERISTICS**

<b>Number of Patients, Male</b>	13
<b>Number of Patients, Female</b>	2
<b>Stage</b>	Metastatic stage IV: 15 patients
<b>Age</b>	Median (range): 68
<b>Number of Prior Systemic Therapies</b>	Median (range): 1
<b>Performance Status: ECOG</b>	0 — 5 1 — 10 2 — 0 3 — 0 Unknown — 0
<b>Other</b>	9 patients: mut-KRAS 3 patients: mut-NRAS 2 patients: mut-BRAF 1 patient Not available

**ADVERSE EVENTS**

<b>Name</b>	<b>NC/NA</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>All grades</b>
Voice alteration	67%	13%	7%	13%	0%	0%	33%
Hypertension	73%	7%	7%	13%	0%	0%	27%
Fatigue	47%	7%	13%	33%	0%	0%	53%

Regorafenib-related grade 3 adverse events: asthenia (33%), dysphonia (13%), and hypertension (13%).

Abbreviation: NC/NA, no change from baseline/no adverse event.

**SERIOUS ADVERSE EVENTS**

<b>Name</b>	<b>Grade</b>	<b>Attribution</b>
Diarrhea	3	Probable
Intestinal hemorrhage	3	Probable
Intestinal perforation	5	Probable
Asthenia	3	Probable
Pyrexia <sup>a</sup>	3	Probable
Abdominal pain <sup>a</sup>	3	Unrelated
Liver failure <sup>a</sup>	5	Unrelated
Sudden death	5	Unrelated
Pain NOS	3	Unrelated
Infection	3	Unrelated
Noncardiac chest pain	2	Unrelated

Serious adverse events were reported in 10 (66.7%) of 15 patients.

<sup>a</sup>Two patients.

Abbreviation: NOS, not otherwise specified.

## ASSESSMENT, ANALYSIS, AND DISCUSSION

<b>Completion</b>	Study terminated before completion
<b>Terminated Reason</b>	Did not fully accrue

## INVESTIGATOR'S ASSESSMENT

Level of activity did not meet planned endpoint

For patients with metastatic colorectal cancer (mCRC), combination chemotherapy schedules with oxaliplatin or irinotecan-based doublets or the 5-FU/irinotecan/oxaliplatin (FOLFOXIRI) triple regimen plus a molecularly targeted compound in the first-line setting have been established as the standard of care on the basis of reported clinical efficacy and safety profile. Namely, in the TRIBE trial, FOLFOXIRI plus bevacizumab showed an improved progression-free survival (PFS) and overall survival (OS) when compared with FOLFIRI plus bevacizumab [1]. In the PREVIUM study, the selection of the FOLFOXIRI/bevacizumab triplet in the first-line treatment was considered the best approach due to its potential to maximize the survival benefit and based on the age, PS, and the clinical and molecular high-risk profile of our population.

However, if disease progression occurs shortly or while on FOLFOXIRI plus bevacizumab, other therapeutic options with a different mechanism of action should be considered. Whereas for relapsed wild-type-KRAS mCRC the current standard treatment is chemotherapy plus an anti-epidermal growth factor receptor antibody, for patients whose tumors bear mutated (mut)-KRAS and/or mut-BRAF and whose disease progresses on a first-line combination of FOLFOXIRI/bevacizumab, the choice of optimal systemic therapy has not yet been established. Objective responses and delayed tumor progression have been reported when second-line treatments containing the same cytotoxic agents have been used. However, for the patients with early relapse as well as patients with toxicities of previous exposure to a fluoropyrimidine-based combination regimen, this approach is not feasible [2,3]. In this scenario, switching to a targeted agent such as a multikinase inhibitor is a valid and recommended approach in the current European Society for Medical Oncology and National Comprehensive Cancer Network guidelines. Regorafenib, a U.S. Food and Drug Administration- and European Medicines Agency-approved biological agent in previously treated mCRC, targets a broad range of angiogenic, stromal, and oncogenic kinases including BRAF, which is approved for the treatment of mCRC, based on the results of the randomized phase III CORRECT trial demonstrating improvement in survival [4].

To our knowledge, this is the first prospective interventional study exploring regorafenib as second-line treatment for an mCRC population pretreated with the triplet FOLFOXIRI/bevacizumab, specifically enrolling mut-KRAS or BRAF patients. However, activity did not reach the level seen in later lines of therapy in patients enrolled on the CORRECT pivotal trial [4]. In this study, OS was 6.4 months (95% confidence interval [CI]: 5.8–7.3) in the regorafenib group and 5.0 months (95% CI: 4.4–5.8) in the placebo group. Median progression-free survival was 2.0 months

(95% CI: 1.9–2.3) and 1.7 months (95% CI: 1.7–1.8), respectively. Our data in the study reported here, in second-line, revealed PFS and OS at 2.2 and 3.3 months, respectively.

This disappointing disease control rate compared with the pivotal phase III trial might be explained by the fact that patients included in our trial had some clinical and molecular high-risk and poor prognosis features. Patients harboring tumors bearing mutations in RAS tend to be even less responsive to chemotherapy than a population with wild-type disease. Furthermore, mut-RAS mCRC exhibits a markedly higher cumulative incidence of lung, bone, and brain metastasis [5,6]. In our study, 12 patients (80%) had an RAS mutation. In addition, 13 of 15 patients included had synchronous metastatic liver and/or lung stage IV disease at initial first diagnosis, and had disease progression <1 month after the end of treatment or while on the oxaliplatin-containing first-line therapy. Worse prognostic variables, defined as having a poor Eastern Cooperative Oncology Group performance score, short time from initial diagnosis of metastases to the start of regorafenib, low initial regorafenib dose, >3 metastatic sites, liver metastases, and mut-KRAS profile, independently and negatively affected survival in patients on regorafenib enrolled in the real-life REBECCA trial [7]. Noticeably, and based on these factors, a high-risk prognostic group with a median survival of 2.5 months was identified. Furthermore, they reproduced this predictive pattern in the FAS-CORRECT population, identifying a particularly poor subpopulation with a median OS of 3.4 months. Likewise, in our study, 87% of patients had detectable circulating tumor cells >3 per 7.5 mL before their first-line treatment, this being considered a poor prognostic feature [8–10].

Regarding tolerability, the frequency and severity of adverse events were consistent with the known safety profile of regorafenib and other multikinase inhibitors, and in the expected range regarding the morbidity of patients previously treated with a fluoropyrimidine-based combination plus bevacizumab.

In summary, although stopped prematurely for failing to accrue, on the population analyzed, regorafenib failed to demonstrate clinical activity in patients with very poor prognosis mCRC that progressed following first-line therapy with the triplet FOLFOXIRI plus bevacizumab, although tolerability was acceptable. Median PFS was consistent with what was reported previously in the pivotal phase III CORRECT trial. Several biomarkers have been implemented to define the best therapeutic strategy in mCRC. Unfortunately, none can be related to regorafenib efficacy. Our trial suggests that exploring regorafenib efficacy in earlier line should not be undertaken without better population refinement.

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**DISCLOSURES**

**Manuel Benavides:** Bayer (C/A, H); **Fernando Rivera:** Amgen (C/A, H, RF), Bayer (C/A, H, RF), Roche (C/A, H, RF); **Amelia Lopez-Ladron:**

Roche (C/A); **Rafael Lopez:** Roche (RF); **Enrique Aranda:** Amgen (C/A), Bayer (C/A), Celgene (C/A), Merck (C/A), Roche (C/A), Sanofi (C/A). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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