



Exploratory findings from a prematurely closed international, multicentre, academic trial: RAVELLO, a phase III study of regorafenib versus placebo as maintenance therapy after first-line treatment in RAS wild-type metastatic colorectal cancer

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ABSTRACT

Background In patients with RAS wild-type (WT) metastatic colorectal cancer (mCRC), the role of maintenance therapy after first-line treatment with chemotherapy plus anti-epidermal growth factor receptor (EGFR) monoclonal antibodies (MoAb) is still an object of debate.

Methods We assessed the efficacy and safety of regorafenib as a switch maintenance strategy after upfront 5-fluorouracil-based chemotherapy plus an anti-EGFR MoAb in patients with RAS WT mCRC. RAVELLO was a phase III, international, double-blind, placebo-controlled, academic trial. The primary endpoint was progression-free survival (PFS). Secondary endpoints included overall survival and toxicity. Regorafenib or placebo were administered daily for 3 weeks of 4-week cycle until disease progression or unacceptable toxicity, up to 24 months.

Results The study was stopped prematurely due to slow accrual and lack of funding after the randomisation of 21 patients: 11 in the regorafenib arm and 10 in the placebo arm. The small sample size precludes any statistical analysis. Toxicity was acceptable and consistent with the known regorafenib safety profile. Median PFS was similar in the two arms. However, a subgroup of patients treated with regorafenib experienced a remarkably long PFS. Three patients were progression free at 9 months in the regorafenib arm versus one patient in the placebo arm, whereas at 12 months two regorafenib-treated patients were still progression free versus none in the placebo arm.

Conclusion RAVELLO trial demonstrated that growing financial and bureaucratic hurdles affect the feasibility of independent academic research. Although stopped prematurely and within the limited sample size, RAVELLO suggests that regorafenib has not a

Key questions

What is already known about this subject?

- Clinical evidence supports the role of maintenance treatment with fluoropyrimidine plus bevacizumab following bevacizumab-based regimens.
- There is no consensus about the role of maintenance in patients with RAS wild-type (WT) metastatic colorectal cancer (mCRC) after chemotherapy plus anti-epidermal growth factor receptor (EGFR) monoclonal antibodies (MoAbs).

What does this study add?

- RAVELLO, a phase III, international, double-blind, placebo-controlled, non-profit, academic trial, was the first interventional study exploring in patients with RAS WT mCRC the role of switch maintenance with regorafenib after upfront chemotherapy in combination with an anti-EGFR MoAb.
- RAVELLO trial demonstrated that, despite a strong researchers' commitment, to run a large investigator-initiated trial in an academic environment is complex and burdened by growing financial and bureaucratic hurdles that may dramatically affect feasibility.

major activity in maintenance setting after upfront chemotherapy and anti-EGFR MoAb. However, a subgroup of patients experienced a remarkable long PFS, indicating that a better refinement of the patient population would help to identify subjects that might benefit from a regorafenib personalised approach in the switch maintenance setting.

Key questions

How might this impact on clinical practice?

- ▶ Even though the premature study termination and the limited sample size preclude efficacy analyses, RAVELLO trial suggests that regorafenib has not major activity in the maintenance setting after upfront chemotherapy with an anti-EGFR MoAb.
- ▶ A subgroup of patients experienced a remarkable long progression-free survival, indicating that a better refinement of the patient population would help to identify subjects that might benefit from a personalised approach in the maintenance setting.
- ▶ Independent academic research is the key to address similar questions and claims significant actions to dismantle barriers and the need to be supported.

INTRODUCTION

The ‘continuum of care strategy’ within the landscape of precision medicine has significantly improved the prognosis of metastatic colorectal cancer (mCRC). The introduction of intensive and effective upfront therapies, the improved outcomes after surgery of metastatic lesions and the clinical impact of refinements of molecular selection raise the question of the optimal duration of first-line treatments and the role of maintenance therapy.

Clinical data are currently available in support of maintenance therapy with fluoropyrimidine plus bevacizumab following bevacizumab-based regimens.^{1,2} However, the role of maintenance after chemotherapy plus anti-epidermal growth factor receptor (EGFR) monoclonal antibodies (MoAb) is still object of debate and the optimal deintensified regimen needs to be established.

Data from phase II trials suggest that after an upfront treatment with anti-EGFR-based therapy, alternating phases with treatment breaks or anti-EGFR drug alone³ and de-escalating treatment intensity⁴ might be not inferior in terms of efficacy and are associated with reduced toxicity and improved quality of life. In addition, the VALENTINO trial has recently shown that de-escalating treatment intensity with an anti-EGFR MoAb (panitumumab) is feasible but is associated with inferior progression-free survival (PFS) time when compared with the combination of fluoropyrimidine and panitumumab.⁵

Furthermore, the phase III ERMES study is assessing whether, after a first-line treatment with folinic acid, fluorouracil and irinotecan (FOLFIRI) plus cetuximab, maintenance with cetuximab alone is not inferior in terms of efficacy and has a better toxicity profile compared with the continuation of chemotherapy plus cetuximab until disease progression.⁶

Although effective in molecularly selected patients, long-term treatment with anti-EGFR MoAb is burdened by persistent skin toxicity, clonal selection pressure and, therefore, the emergence of secondary resistance. Mechanisms of acquired resistance to anti-EGFR inhibitors usually arise as a perturbation in a system based on the addiction to EGFR signalling.⁷ Hyperactivation of alternative pathways, such as vascular endothelium growth

factor (VEGF) and angiogenesis, contributes to the emergence of resistant clones. Preclinical data have provided a biological rationale to further investigate the potential efficacy of the sequential administration of antiangiogenic agents after upfront exposure to an EGFR inhibitor, in the context of a switch maintenance strategy.^{8,9}

In this regard, the MACBETH trial provided further insight. This study, although not reaching its primary endpoint, explored the activity of two first-line strategies, both including an intense induction treatment (fluorouracil, leucovorin, oxaliplatin and irinotecan (FOLF-OXIRI)) in combination with cetuximab, followed either by continuing anti-EGFR inhibition with cetuximab alone or by a switch maintenance approach with bevacizumab alone.¹⁰

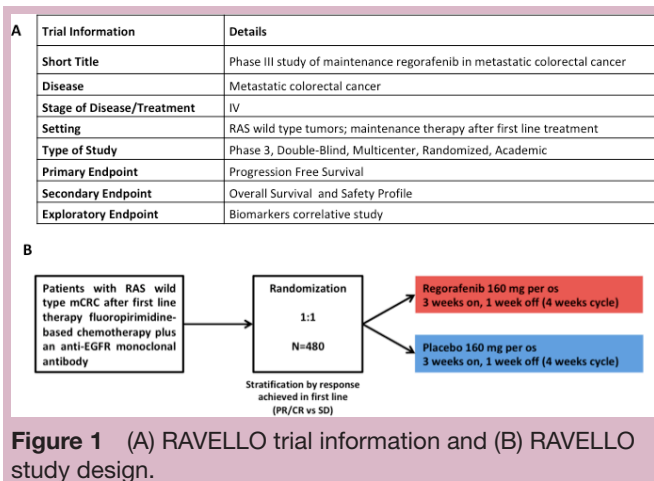
Moreover, the molecular understanding of the complex cross-talk between the EGFR and VEGF pathways, inspired the development of strategies of dual inhibition of EGFR signalling and angiogenesis, with promising activity in preclinical models^{11,12} but controversial outcomes in clinical trials.^{13,14} In this respect, the GERCOR DREAM trial provided intriguing results, demonstrating that, after induction with chemotherapy and bevacizumab, maintenance treatment with a small molecule inhibiting EGFR (erlotinib) in combination with bevacizumab improves survival compared with bevacizumab alone.¹⁵

With regard to switch maintenance strategy, little is known about the role of multikinase inhibitors. Regorafenib is the only multikinase agent approved in CRC for the treatment of metastatic patients refractory to standard therapies. Regorafenib is active on angiogenic (VEGFR-1, VEGFR-2, VEGFR-3, TIE-2), oncogenic (c-KIT, RET, B-RAF) and stromal kinases (PDGFR-B, FGFR1).¹⁶⁻¹⁸ The broad-spectrum activity and the potent antiangiogenic effects render regorafenib a suitable candidate for clinical evaluation in the maintenance setting.

In the context of academic research, our group developed and sponsored the RAVELLO trial, a phase III, international, double-blind, placebo-controlled, investigator-initiated trial aimed to evaluate the efficacy and the safety of regorafenib as maintenance therapy in patients with RAS wild-type (WT) mCRC, after completion of a first-line treatment with fluoropyrimidine-based chemotherapy in combination with an anti-EGFR MoAb, either cetuximab or panitumumab.¹⁹ Despite the efforts provided by all the investigators involved, the study has been prematurely stopped after the randomisation of 21 patients: 11 in the regorafenib arm and 10 in the placebo arm. In the present manuscript, we will discuss the available results and two representative clinical cases.

METHODS**Study design and inclusion and exclusion criteria**

Eligible patients, progression free after a minimum of 4 months up to a maximum of 8 months of first-line treatment, were randomised, in a double-blind fashion, to receive 160 mg regorafenib or placebo orally, 3 weeks



on followed by 1 week off, in 28 days cycles, stratified according to the response achieved in first line (complete and partial response vs stable disease). A maximum of two dose modifications was allowed per study protocol (120 mg–80 mg). Tumour assessments were scheduled every 8 weeks from subject randomisation and tumour response was graded according to the Response Evaluation Criteria in Solid Tumours (RECIST) V.1.1. Patients continued treatment until unacceptable toxicity, consent withdrawal, progressive disease or death, whichever occurred first, up to a maximum of 24 months (figure 1A, B).

Major inclusion criteria were: proved diagnosis of colorectal adenocarcinoma; RAS (ie, KRAS exon 2-3-4 and NRAS at least exon 2-3) WT molecular status, Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1 ; completion of a standard first-line fluoropyrimidine-based chemotherapy in combination with either cetuximab or panitumumab, for a minimum of 4 months (8 cycles) and a maximum of 8 months (16 cycles); having achieved a response (partial or complete) or stabilisation of the disease from the first-line treatment; adequate bone marrow, liver and renal function.

Patients were not eligible in case of interruption of the first-line treatment due to progressive disease; prior treatment with regorafenib; unresolved toxicity attributed to any prior therapy $>$ Grade (G) 1 according to the National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE) V.4.0, excluding oxaliplatin-induced neurotoxicity and anti-EGFR MoAb-induced skin toxicity \leq G1; heart failure $>$ New York Heart Association class 2, unstable angina, new-onset angina (within the last 3 months); history of myocardial infarction within 6 months before the start of the study medication, cardiac arrhythmias requiring antiarrhythmic therapy and uncontrolled hypertension (ie, systolic blood pressure >140 mm Hg or diastolic pressure >90 mm Hg despite optimal medical management).

Sample size calculation and statistical plan

In order to detect a 3-month prolongation of median PFS from randomisation (corresponding to a HR of

progression of 0.67 with 6 months median PFS expected in the control arm), a total of 258 events was required. Considering a 20% dropout rate, the accrual of 480 patients was planned in 30 months.

Demographic and baseline characteristics of the study population, along with clinical data were captured in electronic case report forms, in order to be summarised in a descriptive table by treatment arm (online supplementary table 1). For continuous variables calculation of the mean, SD, range and median were planned to be computed, while calculation of the frequency and per cent were assessed in the case of categorical values. The main endpoint was PFS, defined as the time from the date of randomisation to the date of first observed disease progression (radiological or clinical) or death due to any cause; secondary endpoints were safety, assessed according to NCI-CTCAE V.4.0, and overall survival, defined as the time from randomisation to death due to any cause. The log-rank test stratified by response to first-line treatment and Kaplan-Meier estimates for each treatment group were planned for time to event analyses, using a two-sided alpha of 0.05. Descriptive summary of all safety parameters was scheduled for each treatment, according to NCI-CTCAE V.4.0 category and categorised according to the worst grade (figure 1A, B).

Recruitment phase

In order to recruit 480 patients in 30 months, 48 sites in five European countries (Italy, Spain, Germany, France, Austria) were involved in the trial. In consideration of the regulatory and bureaucratic effort required, a Clinical Research Organisation was hired for the trial conduction. Unpreventable delays related to regulatory and ethical assignments negatively impacted preplanned milestones. Ultimately, of the five countries involved, three were fully activated; one country (France) received a negative opinion from the Competent National Authority and was therefore excluded from the trial, whereas at the time of study closure, in the last country involved (Austria), the activation procedures were not finalised.

The study was conducted in accordance with the Declaration of Helsinki and good clinical practice. All participants were required to provide written informed consent.

The first patient was enrolled in the coordinating centre in September 2014. However, despite the efforts provided, in the active sites, recruitment rates were significantly lower than expected. However, enrolment was stopped due to lack of funding to further support the cost of the study in March 2016, after 26 screening procedures, five screening failures and randomisation of 21 patients, 11 in the regorafenib arm and 10 in the placebo arm. At the time of trial closure, unblinding was authorised in each involved site and patients who had already received at least one dose of regorafenib were permitted to continue the treatment following protocol safety and efficacy assessments, until unacceptable toxicity, consent withdrawal, progressive disease or death, whichever occurred first, up to a maximum of 24 months.

Molecular characterisation and biomarker analysis

Molecular characterisation was retrospectively conducted in patients who obtained long disease control (N=2), using DNA isolated from the formalin fixed paraffin embedded (FFPE) block collected during pretreatment surgery of primary tumour.

The molecular analysis was performed by FoundationOne CDx, a comprehensive next generation sequencing-based assay for detection of alterations in 324 genes and identification of genomic signatures including microsatellite instability (MSI) and tumour mutational burden (TMB).

RESULTS

Although enrolment was closed prematurely and a definitive statement about regorafenib effectiveness in this setting cannot be made, RAVELLO trial has provided some potential clinical relevant information. Demographic and baseline characteristics of randomised patients are summarised in the online supplementary table 1.

Within the limitation of the restricted sample size, in regorafenib arm, the observed rates and the severity of adverse events (AEs) graded according to NCI-CTCAE V.4.0 were consistent with the known safety profile of the drug. No G4–G5 toxicities were registered in the trial. In patients treated with regorafenib, the main G3 AEs were hyperbilirubinaemia and hypertension, observed in 27% and 18% cases, respectively. Grade 3 fatigue and hyperlipasemia occurred with a similar rate in the two arms ($\approx 10\%$) and, intriguingly, no G3 skin reactions (ie, rash and hand foot skin reaction (HFSR)) was observed in both arms while G1–G2 events were comparable in regorafenib and placebo arms (54% vs 60%). One serious AE, sepsis due to bacterial infection requiring hospitalisation, occurred in the regorafenib arm, but was judged not related to the study drug (table 1).

Ten out of 21 patients required at least one dose modification due to AEs: three in placebo (30%) and seven in regorafenib arm (64%). All dose reductions occurred in the first three cycles of treatment. In the placebo arm, three patients required one dose level reduction due to hyperlipasemia, hypothyroidism and musculoskeletal pain, while in the regorafenib arm, five patients required one dose level reduction due to hypertension (N=2) and hyperbilirubinaemia (N=3) and two patients required a two-dose level reduction due to musculoskeletal pain and fatigue, respectively (table 2).

Treatment was discontinued due to AEs in two patients (9%): one in placebo arm, due to musculoskeletal pain and one in regorafenib arm due to hyperbilirubinaemia. In 18 patients (86%), treatment was discontinued due to progressive disease: nine in placebo arm and nine in regorafenib arm. One patient treated with regorafenib completed the trial, having received the maximum number of months of treatment specified by the protocol (see below a detailed description of patient outcome).

At a median follow-up of 31.3 months (95% CI 30.1 to 32.5), median PFS was 2.6 months (95% CI 2.0 to 3.2) in the regorafenib arm and 3.6 months (95% CI 2.0 to 5.3) in the placebo arm, whereas median overall survival was not reached in the two arms. Median number of cycles was 3.0 (95% CI 1.90 to 11.0) in the experimental arm and 3.5 (95% CI 2.58 to 6.42) in the control arm. Disease control rate, defined as the percentage of patients who have achieved response and stabilisation of the disease per RECIST V.1.1, was 55% in the regorafenib arm and 50% in the placebo arm (online supplementary table 2).

Notably, a subgroup of patients treated with regorafenib registered a remarkable long PFS (figure 2). In particular, in the regorafenib arm, three patients were progression free at 9 months compared with one patient in the placebo arm (progression free rate (PFR) at 9 months: 27% and 10%, respectively) and two patients were progression free at 12 months compared with none in placebo arm (PFR at 12 months 18% and 0%, respectively). Worthy of note, the two patients free of progression at 12 months shared some clinical features of worse prognosis: right-sided primary location, poorly differentiated (G3) tumours and metastatic disease at diagnosis. Both had measurable disease at study entry, having obtained stabilisation of the disease as the best response from first-line treatment (table 3). Intriguingly, one of them completed the planned 24 months of study treatment and is still free of progression as of 1 March 2019.

Patients' cases presentation

Patient 2001

In May 2014, a 67-year-old Caucasian man, ECOG performance status 0, receiving oral hypoglycaemic agents for diabetes mellitus, presented with a 2-month history of unintentional weight loss (approximately 15 kg). Diagnostic workup included a CT scan, showing thickening of the right colon, several bilateral centimetric lung lesions and left lateral-cervical lymphadenopathy. A caecal mass was seen at colonoscopy with the biopsy that was diagnostic for G3 adenocarcinoma with signet ring cell features. In June 2014, the patient underwent right hemicolectomy. Histological examination confirmed the diagnosis of G3 adenocarcinoma with signet ring cell features, stage pT3 pN0 (0/37) cM1 (IV stage disease). The molecular assessment of the tumour revealed KRAS and NRAS WT status. The patient received 12 cycles of first-line treatment with FOLFIRI+ cetuximab from October 2014 to April 2015 obtaining as best response disease stabilisation. He was enrolled in the RAVELLO trial and on 21 April 2015 randomised to the regorafenib arm. The patient received a total of 21 cycles, at full dose. No dose modification was required and no major AE was observed. After 5 months of treatment, G1 HFSR and G2 hypophosphataemia were registered and managed with adequate supportive care. In March 2016, at the time of the premature RAVELLO closure, treatment was ongoing and, considering the

Table 1 Adverse events according to NCI-CTCAE V.4.0

Adverse events	Regorafenib (N=11)						Placebo (N=10)					
	Any grade, N (%)		G1–G2, N (%)		G3, N (%)		Any grade, N (%)		G1–G2, N (%)		G3, N (%)	
Anorexia	0	0	0	0	0	0	1	10	1	10	0	0
Fatigue	6	55	5	45	1	9	6	60	5	50	1	10
Pain	3	27	3	27	0	0	8	80	5	50	3	30
Arthralgia	1	9	1	9	0	0	0	0	0	0	0	0
Disgeusia	1	9	1	9	0	0	0	0	0	0	0	0
Dysphonia	3	27	3	27	0	0	1	10	1	10	0	0
Hypertension	6	55	4	36	2	18	2	20	2	20	0	0
Epistaxis	1	9	1	9	0	0	1	10	1	10	0	0
Nausea	0	0	0	0	0	0	3	30	3	30	0	0
Vomiting	0	0	0	0	0	0	1	10	1	10	0	0
Diarrhoea	2	18	2	18	0	0	3	30	3	30	0	0
Mucositis	2	18	2	18	0	0	0	0	0	0	0	0
Xerosis	0	0	0	0	0	0	1	10	1	10	0	0
Rash	1	9	1	9	0	0	3	30	3	30	0	0
Hand and foot skin reaction	5	45	5	45	0	0	3	30	3	30	0	0
Neuropathia	0	0	0	0	0	0	2	20	1	10	1	10
Sepsis	1	9	0	0	1	9	0	0	0	0	0	0
Fever	1	9	1	9	0	0	0	0	0	0	0	0
Anaemia	0	0	0	0	0	0	1	10	1	10	0	0
Decreased platelets	1	9	1	9	0	0	0	0	0	0	0	0
Hyperbilirubinaemia	3	27	0	0	3	27	0	0	0	0	0	0
Hyperlipasemia	2	18	1	9	1	9	1	10	0	0	1	10
Hypolipasemia	0	0	0	0	0	0	1	10	1	10	0	0
Hyperthyroidism	1	9	1	9	0	0	0	0	0	0	0	0
Hypothyroidism	0	0	0	0	0	0	1	10	1	10	0	0
Hypophosphataemia	1	9	1	9	0	0	0	0	0	0	0	0

CTCAE, Common Terminology Criteria for Adverse Event; NCI, National Cancer Institute.

excellent tolerability and clinical benefit reported, as per protocol, patient continued to receive the study drug. On 16 January 2017, after 21 cycles, a CT scan showed disease progression in the lungs and treatment was discontinued. Thus, PFS from randomisation was 21.2 months. Molecular assessment by FoundationOne CDx was performed using the patient's primary tumour. The analysis revealed high microsatellite (MSI-high) status and high tumour mutational burden (61 Muts/Mb) and identified the following disease-relevant alterations: FBXWT (S668fs*39), PTEN (Y76del), RNF43 (G659fs*41 and R145*), STK11 (E57fs*106), ARID1A (T1917A and G276fs*87) ASXL1 (G645fs*58), CDH1 (F462fs*19), CIC (T1541fs*79), CREBBP (V95fs*29), FAM46C (A232T), FLCN (H429fs*39 and W306*), KDM6A (R1351*), MLH1 (R226*), MLL2 (P2354fs*30), MSH3 (splice site 1897–1G>A, K383fs*32), MSH6 (Y524fs*1, F1088fs*2

and R361H), SDA (R379C) and TP53 (R248Q). Moreover, the following variants of unknown significance were detected: APC (N944T), ARID1A (G187S), AXIN1 (G265fs*149), AXL (H292fs*5), BCOR (R1136C), BRCA2 (A2351T and S1437N), CBL (T231I), CD22 (splice site 1771+2T>C), EPHA3 (K713T), EPHB4 (V330M), ERBB4 (R1273Q), FGFR4 (N228S and R54C), HGF (G375D and R178Q), ID3 (S49T), JAK3 (I955T), KDM5A (E1137fs*13 and R1051Q), LTK (R647Q), MPL (R390C), MTOR (R2193C), NF1 (R1396H), NKX2-1 (S233G), P2RY8 (A188T), PARP1 (S507fs*17), PDGFRB (L726fs*7 and V886M), PIK3C2B (E1507fs*12), PIK3CA (P397H), PIM1 (P309L), POLD1 (A223T and R465W), RET (L1048fs*11), RNF43 (G360D), SDHA (P477S), SGK1 (M17I), SOX9 (M109V), SPOP (A303V), STK11 (E223K), TET2 (S1776F), TSC1 (R908W), WT1 (E479K) and ZNF703 (A514S).

Table 2 Reason for discontinuation and dose reduction levels

Reason for discontinuation	Total (N=21)	Regorafenib (N=11)	Placebo (N=10)
Disease progression	18 (86%)	9 (82%)	9 (90%)
Radiographic progression	17 (81%)	8 (73%)	9 (90%)
Clinical progression	1 (5%)	1 (9%)	0 (0%)
Adverse events	2 (9%)	1 (9%) hyperbilirubinaemia	1 (10%) musculoskeletal pain
Study completion	1 (5%)	1 (9%)	0 (0%)
Dose reduction levels	Total (N=21)	Regorafenib (N=11)	Placebo (N=10)
No dose reduction	11 (52%)	4 (36%)	7 (70%)
160 mg			
One-dose level	8 (38%)	5 (45%)	3 (30%)
120 mg		hyperbilirubinaemia, hypertension	hyperlipasemia, hypothyroidism, musculoskeletal pain
Two-dose level	2 (10%)	2 (18%)	0
80 mg		musculoskeletal pain, fatigue	–

Bold values denote significance.

Patient 2006

A 73-year-old Caucasian man, ECOG performance status 0, with no relevant comorbidities, was diagnosed in September 2014 with adenocarcinoma of the right colon and underwent right hemicolectomy, stage pT3 pN2 (7/18) cMx. CT scan revealed multiple centimetric implants of peritoneal carcinomatosis (stage IV disease). Molecular analysis revealed WT KRAS and NRAS status. From November 2014 to October 2015 the patient received 12 cycles of first-line treatment with FOLFOX+panitumumab, obtaining disease stabilisation per RECIST v1.1 criteria. The patient was enrolled in the RAVELLO trial and on 17 November 2015 was randomised to receive regorafenib. During the first weeks of cycle one of treatment, the patient experienced G3 hyperbilirubinaemia, G2 asthenia and G2 diarrhoea. Study drug was temporarily interrupted and restored after AE resolution with one-dose level reduction (120 mg). In March 2016,

the trial was prematurely closed but, in consideration of the clinical benefit and of the good tolerability, as per protocol, the patient continued to receive regorafenib. The patient experienced G2 HFSR after six cycles managed with 1 week dose delay and no further dose modification; G2 hypertension occurred after 12 cycles, managed with adequate medical treatment. The patient received in total 24 cycles of regorafenib with no other relevant toxicity. The subject obtained as best response disease stabilisation. On 10 November 2017, after 24 months, treatment was discontinued, as per protocol. The patient is currently without any anticancer therapy and free of disease progression with an overall PFS of 39.5 months since being randomised in the RAVELLO trial. Molecular assessment by FoundationOne CDx panel was performed using the FFPE block from the patient's primary tumour. Due to the inadequacy of the tumour specimen, the analysis failed.

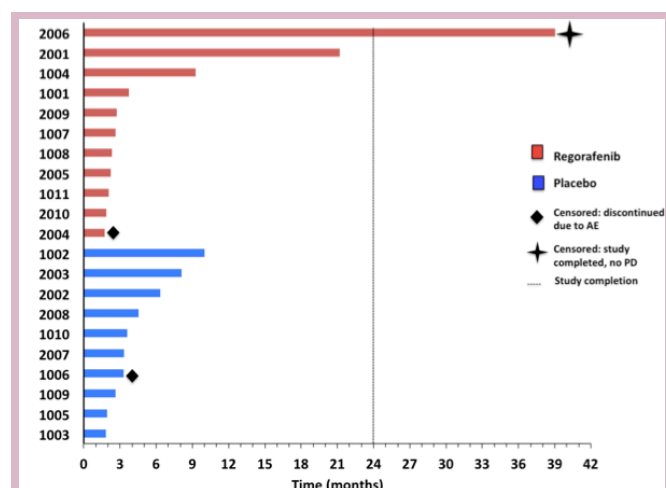


Figure 2 Swimmers plot of progression-free survival of patients in regorafenib arm (red) and placebo arm (blue).

DISCUSSION

The RAVELLO trial was the first randomised study to explore in patients with RAS WT mCRC the role of switch maintenance with regorafenib after upfront chemotherapy in combination with anti-EGFR MoAb. RAVELLO trial demonstrated that, despite a strong commitment by all investigators, to run a large scale, investigator-initiated trial in five different European countries by a completely academic institution is a complex enterprise, challenged and burdened by growing financial and bureaucratic hurdles that may dramatically affect its feasibility. However, independent academic research is a key factor for addressing relevant clinical needs in cancer therapy. Therefore, significant actions are required from legislative and regulatory authorities, industries, academia and patient advocacy organisations in order to dismantle barriers and foster non-profit clinical research in cancer.

Table 3 Summary of clinical and molecular features of a ‘long responder’ patient

Patient	Clinical details	Molecular information
2001	Metastatic disease at diagnosis right-sided primary location poorly differentiated (G3) tumours	Microsatellite status high (MSI-high) Tumour mutational burden high (61 Muts/Mb) FBXWT (S668fs*39), PTEN (Y76del), RNF43 (G659fs*41 and R145*), STK11 (E57fs*106), ARID1A (T1917A and G276fs*87), ASXL1 (G645fs*58), CDH1 (F462fs*19), CIC (T1541fs*79), CREBBP (V95fs*29), FAM46C (A232T), FLCN (H429fs*39 and W306*), KDM6A (R1351*), MLH1 (R226*), MLL2 (P2354fs*30), MSH3 (splice site 1897–1G>A, K383fs*32), MSH6 (Y524fs*1, F1088fs*2, R361H), SDA (R379C), TP53 (R248Q). APC (N944T), ARID1A (G187S), AXIN1 (G265fs*149), AXL (H292fs*5), BCOR (R1136C), BRCA2 (A2351T and S1437N), CBL (T231I), CD22 (splice site 1771+2T>C), EPHA3 (K713T), EPHB4 (V330M), ERBB4 (R1273Q), FGFR4 (N228S and R54C), HGF (G375D and R178Q), ID3 (S49T), JAK3 (I955T), KDM5A (E1137fs*13 and R1051Q), LTK (R647Q), MPL (R390C), MTOR (R2193C), NF1 (R1396H), NKX2-1 (S233G), P2RY8 (A188T), PARP1 (S507fs*17), PDGFRB (L726fs*seven and V886M), PIK3C2B (E1507fs*12), PIK3CA (P397H), PIM1 (P309L), POLD1 (A223T and R465W), RET (L1048fs*11), RNF43 (G360D), SDHA (P477S), SGK1 (M17I), SOX9 (M109V), SPOP (A303V), STK11 (E223K), TET2 (S1776F), TSC1 (R908W), WT1 (E479K) and ZNF703 (A514S).

The premature study termination and the subsequent limited number of patients enrolled preclude any statistical analysis of the RAVELLO trial. However, a descriptive analysis suggests that, although tolerability was acceptable and in line with the known regorafenib safety profile, in the overall unselected population of patients with RAS WT mCRC, regorafenib has little clinical activity in the switch maintenance setting after the completion of upfront 5-fluorouracil-based chemotherapy in combination with an anti-EGFR MoAb. It is of note that two out of 11 patients in the regorafenib arm experienced a remarkably long PFS period. These patients had peculiar clinical features such as metastatic disease at diagnosis, right-sided, poorly differentiated primary tumours.

A retrospective molecular analysis using FoundationOne CDx panel on FFPE primary tumours of patients with long PFS was performed in order to identify potential molecular alterations associated with regorafenib activity. One specimen was available for the analysis, revealing a hypermutated signature with MSI-H status, high TMB and several gene alterations, mainly associated with the deregulated activity of tumour suppressors involved in DNA repair, chromatin remodelling and cell-to-cell adhesion. Intriguingly, in the same sample, gene alterations of AXL, a marker of epithelial to mesenchymal transition (EMT) and PDGFR-B, a stromal kinase, were detected.

These results are consistent with our previous findings suggesting that, among chemorefractory patients with mCRC treated with regorafenib, there is a subgroup of ‘long-responders, which highly benefits from treatment. As previously reported, although extensive molecular characterisation by next-generation sequencing did not clearly identified single predictive biomarkers of response to regorafenib, molecular features that are associated with

epithelial to mesenchymal transition (including GAS6 amplification and SMAD4 mutation) or HER2 gene alterations (including gene amplification and activating gene mutations) could play a role in regorafenib sensitivity or resistance, respectively.^{20 21}

Data coming from a retrospective transcriptomic characterisation by gene expression of chemorefractory patients enrolled in phase III CORRECT trial are in line with the present results.^{18 22} Patients stratification according to Marisa *et al* molecular classification²³ showed that in patients treated with regorafenib within the CORRECT trial a shorter PFS was observed in ‘high-risk’ subgroups (C4 and C6) compared with the ‘low-risk’ subgroups (C1, C2, C3 and C5). In particular, C4 and C6 are defined as poor prognosis subgroups, both associated with downregulation of cell growth, death pathways and with upregulation of EMT and motility pathways.²³

Taken together, these findings suggest that responsiveness to regorafenib might not be predicted by a single actionable molecular alteration but rather by the presence of a molecular signature, presumably associated with EMT and mesenchymal phenotype. These hypothesis-generating results should be validated by further investigations in a prospective manner.

In conclusion, a better refinement of patients’ population might help to identify subjects that would benefit from a personalised approach with regorafenib in the switch maintenance setting. Independent academic research is the key to address similar questions and must be supported and promoted.

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