Sorafenib and mFOLFOX6 for Metastatic Colorectal Cancer

Sorafenib in Combination with Oxaliplatin, Leucovorin, and Fluorouracil (modified FOLFOX6) as First-line Treatment of Metastatic Colorectal Cancer: The RESPECT Trial

Josep Tabernero,1 Rocio Garcia-Carbonero,2 James Cassidy,3 Alberto Sobrero,4 Eric Van Cutsem,5 Claus-Henning Köhne,6 Sabine Tejpar,5 Oleg Gladkov,7 Irina Davidenko,8 Ramon Salazar,9 Liubov Vladimirova,10 Sergey Cheporov,11 Olga Burdaeva,12 Fernando Rivera,13 Leslie Samuel,14 Irina Bulavina,15 Vanessa Potter,16 Yu-Lin Chang,17 Nathalie A. Lokker,17 and Peter J. O'Dwyer18

Authors’ Affiliations

1Vall d’Hebron University Hospital and Vall d’Hebron Institute of Oncology (VHIO), Universitat Autònoma de Barcelona, Barcelona, Spain; 2Hospital Universitario Virgen del Rocio – Instituto de Biomedicina de Sevilla [IBIS (Universidad de Sevilla, CSIC, HUVR)], Sevilla, Spain; 3Beatson Laboratories, Glasgow UK*; 4Oncologia Medica, Genova, Italy; 5University Hospitals Leuven and KU Leuven, Belgium; 6University Oldenburg, Oldenburg, Germany; 7Chelyabinsk Regional Clinical Oncology Center, Chelyabinsk, Russia; 8Clinical Oncology Center #1, Krasnodar, Russia; 9Instituto Catalán de Oncología, Barcelona, Spain; 10Rostov Research Institute of Oncology, Russia; 11Regional Clinical Oncology Hospital, Yaroslavl, Yaroslavl, Russia; 12Arkhangelsk Regional Clinical Oncology Center, Arkhangelsk, Russia; 13Hospital Marques de Valdecilla, Santander, Spain; 14Aberdeen Royal Infirmary, Aberdeen, UK; 15Sverdlovsk Regional Oncology Center, Ekaterinburg, Russia; 16Nottingham University Hospital NHS Trust, Nottingham, UK; 17Onyx Pharmaceuticals, South San Francisco, CA, USA; 18Abramson Cancer Center, Philadelphia, PA, USA.

*Dr. James Cassidy is currently with Roche Pharmaceuticals, Nutley, NJ, USA
Sorafenib and mFOLFOX6 for Metastatic Colorectal Cancer

Running title: Sorafenib and mFOLFOX6 for Metastatic Colorectal Cancer

Keywords: metastatic colorectal cancer, sorafenib, oxaliplatin, leucovorin, and fluorouracil

Financial Support
Sponsored by Bayer Healthcare LLC and Onyx Pharmaceuticals, Inc.

Corresponding author
Josep Tabernero, MD, PhD
Medical Oncology Department
Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology (VHIO)
Universitat Autònoma de Barcelona
P. Vall d'Hebron 119-129
08035 Barcelona, Spain
Tel +34 93 489 4301
Fax +34 93 274 6059
Email: jtabernero@vhio.net

Disclosures
OB, FR, TS, and EVC have received research funding from Onyx Pharmaceuticals and Bayer.
NL and YLC are employees of Onyx Pharmaceuticals and own stock.
RGC, AS, BI, and TS have consultancy or advisory relationship with Bayer.
AS has received honoraria from Bayer.
Sorafenib and mFOLFOX6 for Metastatic Colorectal Cancer

**Trial Registry ID:** ClinicalTrial.gov NCT00865709

**Word count (excluding references):** 3188

**Tables:** 4

**Figures:** 2

**References:** 50

**Supplementary material:** Supplementary Appendix, Tables A1, A2, and A3
Sorafenib and mFOLFOX6 for Metastatic Colorectal Cancer

**Statement of Translational Relevance**

Fluorouracil-based treatment regimens have provided incremental improvements in outcomes for patients with metastatic colorectal cancer (mCRC). Adding targeted therapies to these regimens may provide additional benefit. Monoclonal antibodies that target signaling pathways associated with cellular differentiation, proliferation, and survival have been developed in mCRC, with epidermal growth factor and vascular endothelial growth factor being key targets. Targeting a broader spectrum of molecules involved in CRC cell proliferation and death, such as receptor and intracellular tyrosine kinases, may confer anti-cancer activity with less risk of tumor resistance. Sorafenib is an oral multikinase inhibitor that targets both intracellular kinases and cell surface receptor kinases. A randomized, double-blind, placebo-controlled phase II trial was carried out to assess the combination of sorafenib with modified FOLFOX6 (leucovorin, oxaliplatin, and fluorouracil) as a first-line therapy in patients with mCRC.
Sorafenib and mFOLFOX6 for Metastatic Colorectal Cancer

Abstract

Purpose: This randomized, double-blind, placebo-controlled, phase IIb study evaluated adding sorafenib to first-line modified FOLFOX6 (mFOLFOX6) for metastatic colorectal cancer (mCRC).

Patients and Methods: Patients were randomized to sorafenib (400 mg BID) or placebo, combined with mFOLFOX6 (oxaliplatin 85 mg/m²; levo-leucovorin 200 mg/m²; fluorouracil 400 mg/m² bolus and 2400 mg/m² continuous infusion) every 14 days. Primary endpoint was progression-free survival (PFS). Target sample was 120 events in 180 patients for >85% power (2-sided $\alpha=0.20$) to detect a hazard ratio (HR)=0.65.

Results: Of 198 patients randomized, median PFS for sorafenib plus mFOLFOX6 was 9.1 versus 8.7 months for placebo plus mFOLFOX6 (HR=0.88, 95% CI 0.64–1.23; $P=0.46$). There was no difference between treatment arms for overall survival (OS). Subgroup analyses of PFS and OS showed no difference between treatment arms by KRAS or BRAF status (mutant and wild-type). The most common Grade 3/4 adverse events in the sorafenib and placebo arms were neutropenia (48% v 22%), peripheral neuropathy (16% v 21%), and Grade 3 hand-foot skin reaction (20% v 0%). Treatment discontinuation due to adverse events was 9% and 6%, respectively. Generally, dose intensity (duration and cumulative doses) was lower in the sorafenib arm than in the placebo arm.

Conclusion: This study did not detect a PFS benefit with the addition of sorafenib to first-line mFOLFOX6 for mCRC. KRAS and BRAF status did not appear to impact treatment outcomes but the subgroups were small. These results do not support further development of sorafenib in combination with mFOLFOX6 in molecularly-unselected patients with mCRC.
Introduction

Several fluorouracil-based chemotherapy regimens have been successfully developed for patients with metastatic colorectal cancer (mCRC). Incremental improvements in response rates, progression-free survival (PFS), and overall survival (OS) have been observed with fluorouracil in combination with leucovorin and oxaliplatin (FOLFOX), leucovorin and irinotecan (FOLFIRI), and leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI). Nonetheless, survival remains limited with a 5-year rate of less than 8% (1). Strategies to further improve outcomes have focused on adding targeted therapies to established regimens.

Advances in our understanding of the molecular basis of cancer proliferation, angiogenesis, and metastasis enabled the development of therapies that target signaling pathways associated with cellular differentiation, proliferation, and survival. Among these, epidermal growth factor (EGF) and vascular endothelial growth factor (VEGF) are key targets (1). The addition of monoclonal antibodies (mAbs) that target tyrosine kinase (TK) activity (ligands or receptors) to mCRC chemotherapy regimens improved clinical outcomes with acceptable toxicity. These include bevacizumab (inhibits VEGF) (2-5), and the EGF receptor (EGFR) inhibitors cetuximab and panitumumab (6-9). Nonetheless, response can be absent if the target is not a disease driver, and resistance can be present at the start of treatment or can emerge when tumor or stromal cells switch to alternative pathways. The constitutive \textit{KRAS} and \textit{BRAF} mutations confer resistance to cetuximab and panitumumab, and \textit{KRAS} is now a valid biomarker for cetuximab and panitumumab (10). Approximately 40% of patients with CRC have a \textit{KRAS} mutation, meaning a significant proportion will not be eligible for EGFR inhibitors (10).

Targeting a broader spectrum of molecules involved in CRC cell proliferation and death, such as receptor and intracellular TKs, may confer anti-cancer activity with less risk of resistance (11). Sorafenib is an oral multikinase inhibitor that targets intracellular kinases (CRAF, BRAF, mutant
Sorafenib and mFOLFOX6 for Metastatic Colorectal Cancer

BRAF), as well as cell surface receptor kinases, including platelet-derived growth factor receptor (PDGFR), VEGFR-1–3, stem cell factor receptor (KIT), and Feline McDonough Sarcoma (FMS)-related tyrosine kinase 3 (FLT3) (12, 13). Clinical efficacy and tolerability of sorafenib have been shown in renal cell carcinoma (14) and hepatocellular carcinoma (15, 16). Preclinical evidence indicates the primary target of sorafenib in renal cell carcinoma is angiogenesis via VEGFR, whereas in hepatocellular carcinoma, cell proliferation and survival are targeted via the RAF/MEK/ERK pathway, and angiogenesis via VEGFR and PDGFR (12, 17, 18).

Preclinical studies also demonstrated the activity of sorafenib against colon cancer cells, but also indicated differential targeting of cell proliferation and/or angiogenesis by tumor model (12, 19-21). Early clinical studies demonstrated the feasibility of combining sorafenib with chemotherapies used in mCRC, such as irinotecan, oxaliplatin, and 5-fluorouracil/leucovorin, with encouraging activity in solid tumors including mCRC (22-24). In a phase I study of 37 patients with advanced solid tumors, 7/9 patients with CRC treated with oxaliplatin (130 mg/m² on Day 1 of a 3-week cycle) and the standard sorafenib dose (400 mg twice daily [BID] continuously) achieved stable disease for at least 6 weeks (23).

Here we present results from a phase IIb, double-blind, placebo-controlled, randomized trial that assessed the addition of sorafenib to first-line modified FOLFOX6 (mFOLFOX6) in patients with mCRC. The standard sorafenib regimen (400 mg BID continuously) was used based on the collective results from the phase I combination studies (22-24) as well as its proven benefit in other difficult-to-treat adenocarcinomas (14-16). Modified FOLFOX6 was chosen because it was the most commonly used FOLFOX regimen across the various centers and countries of this international study. The objective was to determine whether efficacy and tolerability results would support a phase III confirmatory trial.
Sorafenib and mFOLFOX6 for Metastatic Colorectal Cancer

**Patients and Methods**

**Patients**

Eligible patients were ≥18 years old, with histologically confirmed, measurable metastatic adenocarcinoma of the colon or rectum (stage IV) (25), and an Eastern Cooperative Oncology Group (ECOG) performance status 0–1. Prior radiotherapy was allowed, but at least 1 measurable, non-irradiated, metastatic lesion was required, as was a tumor tissue sample for analysis of *KRAS* and *BRAF* mutations. Patients who had received prior chemotherapy for metastatic disease were not eligible, nor were patients with brain metastases, active cardiac disease, or serious bone marrow, liver, or renal dysfunction. Patients who had received adjuvant treatment for CRC, including a FOLFOX regimen, were eligible provided that they had completed treatment at least 12 months before randomization. The protocol was approved by the independent ethics committees/institutional review boards of all participating sites or countries. The trial was conducted according to Good Clinical Practice Guidelines and in accordance with the Declaration of Helsinki. All patients provided written informed consent. The study is registered at ClinicalTrials.gov (NCT00865709).

**Study Design**

This was a phase IIb, randomized, double-blind trial conducted at centers in Belgium, Romania, Russia, Spain, the United Kingdom, and the United States. Patients were stratified by radiologic evidence of liver involvement and number of metastatic sites (<3 or ≥3) and randomly assigned (1:1) to mFOLFOX6 plus sorafenib or matching placebo.

**Treatment**

The mFOLFOX6 regimen was administered every 14 days and consisted of oxaliplatin, levo-leucovorin (or leucovorin if levo-leucovorin not available), and fluorouracil. On Day 1 of each 14-day cycle, patients received oxaliplatin 85 mg/m², levo-leucovorin 200 mg/m², then a fluorouracil
Sorafenib and mFOLFOX6 for Metastatic Colorectal Cancer

400 mg/m² bolus followed by a 2400 mg/m² continuous infusion (46–48 hours). All patients received prophylactic anti-emetic treatment with intravenous dexamethasone and a 5-hydroxytryptamine-3 antagonist 30 minutes prior to each infusion. Sorafenib and the matching placebo were initiated on Day 1 at 400 mg BID. Dose reductions of sorafenib/placebo were required for hand-foot skin reaction (HFSR, Grades 2/3), hypertension (symptomatic Grade 2 and Grades 3/4), proteinuria (>2g/24 hours), hematologic toxicities (Grades 3/4), or other Grade 3/4 toxicities associated with sorafenib/placebo.

In the case of dose modification or discontinuation of 1 study drug (oxaliplatin, fluorouracil/levo-leucovorin, or sorafenib or placebo), administration of the other study drugs could be continued at the protocol-specified doses. Any patient who continued treatment with at least 1 study drug was considered on study.

Study Endpoints

The primary endpoint was PFS. Secondary endpoints included OS, time to progression (TTP), overall response rate (ORR), duration of response (DOR), safety, and tolerability. Tumor response was investigator assessed and evaluated radiologically at baseline and every 8 weeks using Response Evaluation Criteria in Solid Tumors (RECIST) (26). Active follow-up was extended to patients who discontinued treatment without disease progression. Adverse events (AEs) were graded using Common Terminology Criteria for Adverse Events (version 3.0). Serious AEs (SAEs) included events that resulted in death, were life-threatening, required or extended hospitalization, or resulted in persistent or significant disability.

Statistical Analyses

Analysis of PFS was based on the log-rank test. Based on historical data, the expected PFS in the control arm was 8 months (4). A sample size of 120 events would provide >85% power with...
Sorafenib and mFOLFOX6 for Metastatic Colorectal Cancer

a 2-sided $\alpha = 0.20$, assuming a target hazard ratio (HR) of 0.65 between sorafenib and placebo. The target study population was 180 patients. Analysis of OS was planned after 120 deaths.

Time-to-event endpoints were analyzed by the Kaplan-Meier method in the intent-to-treat (ITT) population. For PFS, patients without documentation of progression or death at the time of analysis were censored at final tumor assessment or post-randomization visit; patients who initiated non-study cancer treatment and were without disease progression were censored at last tumor assessment prior to the start of the new treatment; patients with no post-baseline tumor assessment were censored at Day 1; and patients who experienced progressive disease (PD) or death 18 weeks or longer from the last tumor assessment were censored at the last tumor assessment. A stratified log-rank test with the randomization stratification factors as covariates was used to compare treatment arms, and the relative risk for sorafenib versus placebo was estimated with a stratified Cox regression model.

Secondary analyses of PFS included a per-protocol analysis (patients with no major protocol violations), and a non-stratified analysis. Planned subgroup analyses of PFS and OS were performed using the Kaplan-Meier method and a non-stratified Cox regression for subgroups defined by baseline factors of liver involvement (yes or no), number of metastatic sites (<3 or $\geq 3$), region (East or West), KRAS status (wild-type or mutant), and BRAF status (wild-type or mutant). KRAS and BRAF mutant status was determined by allelic discrimination (Supplementary Appendix) and centrally evaluated at University Hospital Gasthuisberg, Leuven, Belgium (S.T.). Exploratory analyses of PFS and OS were performed for subgroups defined by NRAS and PIK3CA status (wild-type or mutant), age (<65 or $\geq 65$ years), gender, ECOG performance status (0 or 1), disease stage at diagnosis (I–III or IV), and months since initial diagnosis (<2 or $\geq 2$). ORR was compared between groups using the Cochran-Mantel-Haenszel test, adjusting for the stratification factors. Descriptive statistics summarized safety.
Sorafenib and mFOLFOX6 for Metastatic Colorectal Cancer

and tolerability variables, including study drug exposure and AE rates. Statistical analyses were performed with SAS version 9.1 or later (SAS Institute, Cary, NC). The lead author (JT) had full access to study data and analyses, which were available to all authors upon request.

Results

Patient recruitment occurred between March 2009 and February 2010 with 198 patients randomized (Figure 1). Data cut-off for the primary analysis of PFS, response, safety, and tolerability was January 31, 2011. An analysis of OS was subsequently conducted after 123 deaths with a cut-off date of December 1, 2011, and a median follow-up of 22.4 months.

Baseline characteristics were generally balanced between treatment arms (Table 1). Most patients had an ECOG performance status of 1 (64.6%), stage IV disease as initial diagnosis (68.2%), <3 metastatic sites (71.7%), and liver involvement (80.8%). Of note, the sorafenib arm had fewer males compared with the placebo arm (43.3% \( v \) 62.4%), less exposure to adjuvant chemotherapy (7.2% \( v \) 12.9%), and lower rates of KRAS mutations (37.1% \( v \) 48.5%). BRAF mutations were infrequent in both arms (3.1% \( v \) 5.0%).

Efficacy Outcomes

Median PFS was 9.1 months for the sorafenib arm and 8.7 months for the placebo arm (HR=0.88; 95% confidence interval [CI] 0.64–1.23; \( P=0.46 \)) (Figure 2). Similar results were observed in the prespecified subgroup analyses (Table 2). In patients with wild-type KRAS, the median PFS was 9.5 versus 9.2 months, respectively (HR=0.84; 95% CI 0.52–1.36), with corresponding medians of 7.8 versus 7.6 months, respectively, in the mutant KRAS subgroup (HR=0.96; 95% CI 0.59–1.58). In patients with wild-type BRAF, the median PFS was 9.2 versus 9.0 months, respectively (HR=0.91; 95% CI 0.64–1.29), and the median PFS for mutant BRAF was 8.6 versus 7.3 months, respectively (HR=0.89; 95% CI 0.15–5.42).
Sorafenib and mFOLFOX6 for Metastatic Colorectal Cancer

Median OS was 17.6 months in the sorafenib arm and 18.1 months in the placebo arm (HR=1.13; 95% CI 0.79–1.61; \( P = .51 \)). In patients with wild-type \( KRAS \), median OS was 19.9 versus 16.8 months, respectively (HR=0.89; 95% CI 0.54–1.48), and 17.0 versus 19.4 months, respectively, in patients with mutant \( KRAS \) (HR=1.29; 95% CI 0.74–2.24). In patients with wild-type \( BRAF \), median OS was 18.8 versus 18.3 months, respectively (HR=1.09; 95% CI 0.74–1.60), and 13.9 versus 11.9 months, respectively, in patients with mutant \( BRAF \) (HR=0.46; 95% CI 0.09–2.39). Exploratory subgroup analyses showed slightly different outcomes between treatment arms by gender and ECOG status (Table 2). There were no differences in survival outcomes between treatment arms in the \( PIK3CA \) or in the \( NRAS \) subgroups (Supplementary Appendix, Tables A1 and A2).

Median TTP was 9.2 months in the sorafenib arm and 9.0 months in the placebo arm (HR=0.83; 95% CI 0.59–1.17), and the ORR was 46.4% and 60.4%, respectively (Table 3). Partial response was lower in the sorafenib arm compared with mFOLFOX6 alone (44.3% vs 59.4%), but the rate of stable disease was higher (40.2% vs 30.7%). Complete response was achieved by 2 patients in the sorafenib arm and 1 patient in the placebo arm.

Safety and Tolerability

Treatment-related AEs occurring in ≥10% of patients are shown in Table 4. The most common AEs (any grade) in the sorafenib and placebo arms included neutropenia (62% vs 38%), peripheral neuropathy (61% vs 65%), diarrhea (48% vs 35%), nausea (36% vs 47%), HFSR (54% vs 10%), and asthenia (28% vs 19%). Other AEs (any grade) of interest were stomatitis (22% vs 4%), rash (23% vs 9%), and hypertension (19% vs 5%). The most common Grade 3/4 AEs in the sorafenib and placebo arms were neutropenia (48% vs 22%), peripheral neuropathy (16% vs 21%), and HFSR (20% vs 0%). Treatment-related SAEs occurred in 21 (22%) patients in the
sorafenib arm and 16 (16%) patients in the placebo arm. There were 2 treatment-related deaths in the sorafenib arm (1 pancytopenia and 1 renal failure) and 1 in the placebo arm (cardiovascular insufficiency).

More frequent dose interruptions and reductions were observed for sorafenib than placebo (Supplementary Appendix Table A3). The average daily dose of sorafenib was lower than placebo (mean, 553.1 v 728.1 mg), which corresponded to a greater frequency of dose reductions (66.0% v 27.7%) and a shorter mean duration of treatment (30.5 v 33.7 weeks). Similar trends were observed for components of mFOLFOX6, although the magnitude of the difference between treatment arms was less pronounced. Overall, 9.4% of patients discontinued treatment due to AEs in the sorafenib arm compared with 5.9% in the placebo arm.

Discussion
In this randomized phase IIb trial, the addition of sorafenib 400 mg BID to mFOLFOX6 compared with placebo did not demonstrate an improvement in PFS to support a phase III trial. Generally, there was no differential outcome across subgroups, including KRAS and BRAF subgroups. There was also no improvement in TTP or ORR. There were no unexpected toxicities associated with the addition of sorafenib, but there were increases in some Grade 3/4 AE rates, most notably neutropenia and HFSR, which led to increased rates of dose modifications and treatment discontinuations for reasons other than disease progression. Overall, the average daily dose of sorafenib was lower than placebo, and exposure to each of the mFOLFOX6 components was also lower in the sorafenib arm.

While these results allow us to exclude a strong therapeutic benefit with sorafenib plus mFOLFOX6, a number of factors may have influenced the results and should be considered. First, the sample size would have been too small to adequately assess a modest therapeutic
Sorafenib and mFOLFOX6 for Metastatic Colorectal Cancer

benefit. Given the inter- and intra-patient heterogeneity in primary and metastatic CRC tumor types (27, 28), a more modest benefit would not be unexpected for a targeted therapy. Second, use of sorafenib in mCRC may be better suited for regimens that are less active than mFOLFOX6 but more tolerable and where an increase in activity would be more easily detected. Third, the 400 mg BID dose of sorafenib may not have provided sufficient target inhibition, which may have been accentuated by the decrease in dose intensity of both sorafenib and mFOLFOX6 over the course of treatment.

Thus far, results of studies with targeted therapies in combination with mCRC chemotherapy have been mixed, ranging from significant improvements in PFS or OS to decreases in PFS or OS, depending on the chemotherapy regimen and patient population (2-5, 9, 29-31). A number of phase III studies have shown that adding bevacizumab to fluorouracil-based regimens improves PFS with or without a corresponding improvement in OS (2-4, 29), but the magnitude of the benefits have been inconsistent (5). This may be related to the fluorouracil backbone combined with bevacizumab and/or the line of therapy (2-4). Variability in results has also been observed across cetuximab (6, 9, 31) and panitumumab studies (7, 8). It has been hypothesized that inconsistencies in outcomes with mAbs could also be related to their high specificity, which may make them susceptible to resistance through redundant signaling pathways (11). Attempts to broaden activity by combining different mAbs have not proven fruitful in mCRC (32-34).

Results with small-molecule multikinase inhibitors with a broader spectrum of inhibitory targets than mAbs (35) have also been mixed, although limited data are available in addition to the results reported here (36-40). In 2 phase III trials in mCRC, adding vatalanib (targets VEGFR1-3, PDGFRβ, and KIT) to first- or second-line FOLFOX4 did not improve PFS or OS (36, 37), and a phase III study of sunitinib (targets VEGFR1-3, PDGFRα/β, KIT, FLT3, CSF1R, RET) with FOLFIRI failed to demonstrate an improvement in the primary endpoint of PFS (41). Cediranib
Sorafenib and mFOLFOX6 for Metastatic Colorectal Cancer

(targets VEGFR1-3, PDGFRβ, and KIT), has been evaluated with FOLFOX in mCRC in 3 different phase II/III trials (42-44), with only 1 study demonstrating a statistically significant but clinically modest improvement in median PFS (+0.4 months) (45). Nevertheless, other multikinase inhibitors may have potential in mCRC. In a phase III trial, regorafenib (targets VEGFR1-3, Tie-2, PDGFR, FGFR, KIT, RET, and BRAF) provided a survival benefit when added to best supportive care in patients with refractory mCRC (46, 47). It is notable that regorafenib was active in the refractory setting as monotherapy, whereas mCRC studies with other targeted agents lacked single-agent activity or were paired with chemotherapy in the first- or second-line setting.

Several factors may explain the variability in results with targeted therapies in mCRC. It is becoming evident that the genetic profiles of tumors are predictive of treatment response to targeted therapies. In our study, by adding sorafenib to a standard first-line chemotherapy for mCRC, several pathways shown to be critical in mCRC were targeted, like angiogenesis via extracellular TK receptors VEGFR1-3 and PDGFR, as well as downstream protein effectors of TK receptors (e.g., EGFR) including CRAF, BRAF, and mutant BRAF (12, 13, 20, 21). As RAF is targeted by sorafenib and is downstream of RAS, we hypothesized that mCRC patients could potentially derive benefit by the addition of sorafenib independent of KRAS and BRAF gene mutation status. However, this is a highly redundant pathway with complex feedback loops, which makes it unlikely for RAF inhibition alone to be sufficient for antitumoral activity (48).

In the current study, the tumor sample was taken from either the primary or metastatic site, and it does not appear that KRAS or BRAF status had a significant impact on outcomes in patients receiving sorafenib. However, the size of the study population and subgroups limits the interpretation of these data. Sorafenib may be more active with other chemotherapy regimens and/or in more specific patient populations. Although a pharmacokinetic interaction between
Sorafenib and mFOLFOX6 for Metastatic Colorectal Cancer

Sorafenib and oxaliplatin was not detected in a phase I trial of solid tumors (23), some preclinical evidence suggests that sorafenib may reduce cellular uptake of platinum compounds (49). The addition of sorafenib to other mCRC regimens, such as irinotecan alone (50) or FOLFIRI (NCT00839111), are being explored. In addition, studies in various mCRC models showed differential response to sorafenib (12, 20, 21). Sorafenib demonstrated inhibition of tumor growth and angiogenesis in HT-29 colon cells (BRAF V600E mutation), inhibition of tumor growth in HCT-116 cells (activating KRAS mutation), but notably less activity in DLD-1 (activating KRAS mutation) and Colo-205 (BRAF V600E mutation) cells. Further assessment of sorafenib and other targeted therapies across mCRC models may help us to better understand and predict treatment response of primary and metastatic tumors in CRC patients.

In conclusion, the dose and schedule of sorafenib with first-line mFOLFOX6 in this study did not demonstrate a PFS benefit in patients with mCRC to support a phase III trial of similar design. KRAS and BRAF status did not appear to impact response to sorafenib, but patient numbers were small. Further assessment of tumor samples for biomarkers are ongoing and includes gene expression profiling. Although the results of this study do not support further development of sorafenib with this combination in an unselected patient population, they may help to guide the design of future clinical trials in mCRC with targeted therapies focusing on molecularly-characterized populations.
Acknowledgments

This study was supported by Bayer Healthcare Pharmaceuticals and Onyx Pharmaceuticals. The authors would like to thank Melanie Watson, PhD and Michael Raffin (Fishawack Communications) for providing writing and editorial assistance which was funded by Bayer HealthCare Pharmaceuticals and Onyx Pharmaceuticals. EVC and ST are senior investigators of the Fund for Scientific Research Flanders and are supported by the Belgian Foundation against Cancer.
References

Sorafenib and mFOLFOX6 for Metastatic Colorectal Cancer


Sorafenib and mFOLFOX6 for Metastatic Colorectal Cancer


Sorafenib and mFOLFOX6 for Metastatic Colorectal Cancer


Sorafenib and mFOLFOX6 for Metastatic Colorectal Cancer


Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sorafenib + FOLFOX6 (n=97)</th>
<th>Placebo + FOLFOX6 (n=101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean (range)</td>
<td>59.2 (33–82)</td>
<td>60.3 (44–77)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>42 (43.3)</td>
<td>63 (62.4)</td>
</tr>
<tr>
<td>Female</td>
<td>55 (56.7)</td>
<td>38 (37.6)</td>
</tr>
<tr>
<td>Race/ethnicity, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>95 (97.9)</td>
<td>101 (100)</td>
</tr>
<tr>
<td>Asian</td>
<td>2 (2.1)</td>
<td>0</td>
</tr>
<tr>
<td>Region, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>West region*</td>
<td>40 (41.2)</td>
<td>41 (40.6)</td>
</tr>
<tr>
<td>East region†</td>
<td>57 (58.8)</td>
<td>60 (59.4)</td>
</tr>
<tr>
<td>ECOG performance status, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>34 (35.1)</td>
<td>36 (35.6)</td>
</tr>
<tr>
<td>1</td>
<td>63 (64.9)</td>
<td>65 (64.4)</td>
</tr>
<tr>
<td>Stage IV disease at initial diagnosis, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>68 (70.1)</td>
<td>67 (66.3)</td>
</tr>
<tr>
<td>No</td>
<td>28 (28.9)</td>
<td>33 (32.7)</td>
</tr>
<tr>
<td>Missing</td>
<td>1 (1.0)</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td>Metastatic sites, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3</td>
<td>71 (73.2)</td>
<td>71 (70.3)</td>
</tr>
<tr>
<td>≥3</td>
<td>26 (26.8)</td>
<td>30 (29.7)</td>
</tr>
</tbody>
</table>
Sorafenib and mFOLFOX6 for Metastatic Colorectal Cancer

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sorafenib + FOLFOX6 (n=97)</th>
<th>Placebo + FOLFOX6 (n=101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver involvement, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>79 (81.4)</td>
<td>81 (80.2)</td>
</tr>
<tr>
<td>No</td>
<td>18 (18.6)</td>
<td>20 (19.8)</td>
</tr>
<tr>
<td>Prior diagnostic/therapeutic procedure, n (%)</td>
<td>93 (95.9)</td>
<td>99 (98.0)</td>
</tr>
<tr>
<td>Prior adjuvant chemotherapy, n (%)</td>
<td>7 (7.2)</td>
<td>13 (12.9)</td>
</tr>
<tr>
<td>KRAS status, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wild type</td>
<td>52 (53.6)</td>
<td>45 (44.6)</td>
</tr>
<tr>
<td>Mutant</td>
<td>36 (37.1)</td>
<td>49 (48.5)</td>
</tr>
<tr>
<td>Missing</td>
<td>9 (9.3)</td>
<td>7 (6.9)</td>
</tr>
<tr>
<td>BRAF status, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wild type</td>
<td>85 (87.6)</td>
<td>89 (88.1)</td>
</tr>
<tr>
<td>Mutant</td>
<td>3 (3.1)</td>
<td>5 (5.0)</td>
</tr>
<tr>
<td>Missing</td>
<td>9 (9.3)</td>
<td>7 (6.9)</td>
</tr>
</tbody>
</table>

ECOG, Eastern Cooperative Oncology Group; KRAS, Kirsten rat sarcoma viral oncogene homolog

*Spain, United Kingdom, Belgium, United States; †Russia, Romania
Table 2. Progression-free survival and overall survival by planned and exploratory subgroups

<table>
<thead>
<tr>
<th>Subgroup (n)</th>
<th>Median PFS, mo</th>
<th>Median OS, mo</th>
<th>Planned</th>
<th></th>
<th>Exploratory</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sorafenib + mFOLFOX6</td>
<td>Placebo + mFOLFOX6</td>
<td>HR (95% CI)</td>
<td>Sorafenib + mFOLFOX6</td>
<td>Placebo + mFOLFOX6</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Overall (198)</td>
<td>9.1</td>
<td>8.7</td>
<td>0.88 (0.64–1.23)</td>
<td>17.6</td>
<td>18.1</td>
<td>1.13 (0.79–1.61)</td>
</tr>
<tr>
<td>Liver involvement</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (160)</td>
<td>8.9</td>
<td>8.0</td>
<td>0.86 (0.60–1.24)</td>
<td>18.3</td>
<td>18.3</td>
<td>1.06 (0.72–1.56)</td>
</tr>
<tr>
<td>No (38)</td>
<td>11.0</td>
<td>9.7</td>
<td>1.01 (0.44–2.32)</td>
<td>15.8</td>
<td>17.6</td>
<td>1.11 (0.47–2.61)</td>
</tr>
<tr>
<td>No. of metastatic sites</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3 (142)</td>
<td>9.2</td>
<td>8.7</td>
<td>0.85 (0.58–1.25)</td>
<td>20.6</td>
<td>18.7</td>
<td>0.88 (0.56–1.36)</td>
</tr>
<tr>
<td>≥3 (56)</td>
<td>7.4</td>
<td>8.3</td>
<td>0.96 (0.53–1.72)</td>
<td>13.9</td>
<td>16.4</td>
<td>1.88 (1.02–3.47)</td>
</tr>
<tr>
<td>Region</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>East (117)*</td>
<td>7.7</td>
<td>9.0</td>
<td>0.98 (0.64–1.50)</td>
<td>16.4</td>
<td>18.0</td>
<td>1.19 (0.76–1.87)</td>
</tr>
<tr>
<td>West (81)†</td>
<td>9.2</td>
<td>8.0</td>
<td>0.76 (0.46–1.27)</td>
<td>20.2</td>
<td>18.1</td>
<td>0.92 (0.52–1.62)</td>
</tr>
<tr>
<td>KRAS status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wild-type (97)</td>
<td>9.5</td>
<td>9.2</td>
<td>0.84 (0.52–1.36)</td>
<td>19.9</td>
<td>16.8</td>
<td>0.89 (0.54–1.48)</td>
</tr>
<tr>
<td>Mutant (85)</td>
<td>7.8</td>
<td>7.6</td>
<td>0.96 (0.59–1.58)</td>
<td>17.0</td>
<td>19.4</td>
<td>1.29 (0.74–2.24)</td>
</tr>
<tr>
<td>BRAF status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wild-type (174)</td>
<td>9.2</td>
<td>9.0</td>
<td>0.91 (0.64–1.29)</td>
<td>18.8</td>
<td>18.3</td>
<td>1.09 (0.74–1.60)</td>
</tr>
<tr>
<td>Mutant (8)</td>
<td>8.6</td>
<td>7.3</td>
<td>0.89 (0.15–5.42)</td>
<td>13.9</td>
<td>11.9</td>
<td>0.46 (0.09–2.39)</td>
</tr>
<tr>
<td>Exploratory</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 (137)</td>
<td>8.9</td>
<td>7.8</td>
<td>0.85 (0.58–1.27)</td>
<td>18.9</td>
<td>19.5</td>
<td>0.96 (0.62–1.48)</td>
</tr>
</tbody>
</table>
Sorafenib and mFOLFOX6 for Metastatic Colorectal Cancer

<table>
<thead>
<tr>
<th>Subgroup (n)</th>
<th>Median PFS, mo</th>
<th>Median OS, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sorafenib + mFOLFOX6</td>
<td>Placebo + mFOLFOX6</td>
</tr>
<tr>
<td>≥65 (61)</td>
<td>9.2</td>
<td>9.2</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (105)</td>
<td>9.5</td>
<td>7.8</td>
</tr>
<tr>
<td>Female (93)</td>
<td>7.8</td>
<td>10.4</td>
</tr>
<tr>
<td>ECOG status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 (70)</td>
<td>9.5</td>
<td>9.0</td>
</tr>
<tr>
<td>1 (128)</td>
<td>7.6</td>
<td>8.0</td>
</tr>
<tr>
<td>Disease stage at diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I-III (61)</td>
<td>9.2</td>
<td>9.0</td>
</tr>
<tr>
<td>IV (135)</td>
<td>8.9</td>
<td>8.0</td>
</tr>
<tr>
<td>Months since initial diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2 (57)</td>
<td>9.3</td>
<td>9.0</td>
</tr>
<tr>
<td>≥2 (141)</td>
<td>9.1</td>
<td>8.3</td>
</tr>
</tbody>
</table>

*Russia, Romania
†Spain, United Kingdom, Belgium, United States

BRAF, v-raf murine sarcoma viral oncogene homolog B1; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; KRAS, Kirsten rat sarcoma viral oncogene homolog; PFS, progression-free survival; OS, overall survival
Table 3. Secondary efficacy endpoints

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sorafenib + mFOLFOX6 (n=97)</th>
<th>Placebo + mFOLFOX6 (n=101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median TTP, months</td>
<td>9.2</td>
<td>9.0</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.83 (0.59–1.17)</td>
<td></td>
</tr>
<tr>
<td>Overall response rate, %</td>
<td>46.4 (36.2–56.8)</td>
<td>60.4 (50.2–70.0)</td>
</tr>
<tr>
<td>Best response, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response (CR)</td>
<td>2 (2.1)</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>43 (44.3)</td>
<td>60 (59.4)</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>39 (40.2)</td>
<td>31 (30.7)</td>
</tr>
<tr>
<td>Progressive disease (PD)</td>
<td>5 (5.2)</td>
<td>7 (6.9)</td>
</tr>
<tr>
<td>Median duration of response, months†</td>
<td>7.5</td>
<td>6.7</td>
</tr>
</tbody>
</table>

*Patients with missing or non-evaluable best response data are not listed.

†Only responders (CR or PR) are included in this summary.

CI, confidence interval; HR, hazard ratio; TTP, time to progression
Sorafenib and mFOLFOX6 for Metastatic Colorectal Cancer

Table 4. Treatment-related adverse events reported in ≥10% (any grade) of patients

<table>
<thead>
<tr>
<th></th>
<th>Sorafenib + FOLFOX6 (N=97)</th>
<th>Placebo + FOLFOX6 (N=101)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>60 (62)</td>
<td>47 (48)</td>
</tr>
<tr>
<td>Peripheral neuropathy*</td>
<td>59 (61)</td>
<td>16 (16)</td>
</tr>
<tr>
<td>Hand-foot skin reaction†</td>
<td>52 (54)</td>
<td>19 (20)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>47 (48)</td>
<td>9 (9)</td>
</tr>
<tr>
<td>Nausea</td>
<td>35 (36)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>27 (28)</td>
<td>6 (6)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>24 (25)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>23 (24)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Rash</td>
<td>22 (23)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>21 (22)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>21 (22)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>18 (19)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>18 (19)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>18 (19)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Anemia</td>
<td>17 (18)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>13 (13)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>12 (12)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Erythema</td>
<td>11 (11)</td>
<td>2 (2)</td>
</tr>
</tbody>
</table>

*Peripheral neuropathy, peripheral sensory neuropathy, dysesthesia, neurotoxicity, paraesthesia

†Grade 3 is the most severe grade.
Figure Legends

Figure 1. Patient disposition (January 31, 2011).

Figure 2. Survival outcomes by the Kaplan-Meier Method intent-to-treat patient population: (A) progression-free survival (data cut-off January 31, 2011), and (B) overall survival (data cut-off December 1, 2011).
Figure 1

Screened (n=230)
- Excluded (n=32)
  - Did not meet eligibility criteria (n=22)
  - Declined to participate (n=3)
  - Due to AE (n=3)
  - Other (n=4)

Randomized, ITT (n=198)

Randomized to placebo (n=101)
- Received study treatment (n=101)

Randomized to sorafenib (n=97)
- Received study treatment (n=97)

Lost to follow-up (n=0)
Discontinued treatment (n=85)
- Progressive disease (n=49)
- AEs (n=9)
- Death (n=6)
- Patient consent withdrawn, investigator decision, or surgery (n=21)

Lost to follow-up (n=0)
Discontinued treatment (n=85)
- Progressive disease (n=65)
- AEs (n=6)
- Death (n=2)
- Patient consent withdrawn, investigator decision, or surgery (n=12)

Analysis

ITT (n=101)
- Safety* (n=101)
  - Per protocol† (n=90)
    - Excluded from analysis (n=11)
      - Eligibility violation (n=1)
      - Non-protocol anticancer therapy (n=5)
      - Other (n=5)

Analysis

ITT (n=97)
- Safety* (n=97)
  - Per protocol† (n=82)
    - Excluded from analysis (n=15)
      - Eligibility violation (n=2)
      - Non-protocol anticancer therapy (n=11)
      - Other (n=2)

*Received study treatment
†No major protocol violations
AE, adverse event; ITT, intent to treat
Figure 2

A

Proportion Event Free

PFS events, n
PD, n
Deaths, n
Median PFS, mo
HR (95% CI)
P value
Sorafenib+ mFOLFOX6
87
59
8
9.1
0.88 (0.64–1.23)
.46
Placebo+ mFOLFOX6
82
77
5
8.7

No. at risk

Months from Randomization
Sorafenib
97
78
59
43
14
1
0
Placebo
101
90
72
46
11
0
0

B

Proportion Event Free

Deaths, n
Median OS, mo
HR (95% CI)
P value
Sorafenib+ mFOLFOX6
62
17.6
1.13 (0.79–1.61)
.51
Placebo+ mFOLFOX6
61
18.1

No. at risk

Months from Randomization
Sorafenib
97
90
84
78
69
56
47
34
7
2
0
Placebo
101
98
90
82
71
58
50
38
8
1
0

CI, confidence interval; HR, hazard ratio; OS, overall survival; PD, progressive disease; PFS, progression-free survival.
Sorafenib in Combination with Oxaliplatin, Leucovorin, and Fluorouracil (modified FOLFOX6) as First-line Treatment of Metastatic Colorectal Cancer: The RESPECT Trial

Josep Tabernero, Rocio Garcia-Carbonero, James Cassidy, et al.

Clin Cancer Res  Published OnlineFirst March 26, 2013.

Updated version
Access the most recent version of this article at:
doi:10.1158/1078-0432.CCR-13-0107

Author Manuscript
Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.