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Review

Antiangiogenic Tyrosine Kinase Inhibitors in Metastatic Colorectal Cancer: Focusing on Regorafenib

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Abstract. *The progress of metastatic colorectal cancer (mCRC) depends essentially on two signaling pathways: the first mediated by vascular endothelial growth factor (VEGF) and the second by epidermal growth factor receptor (EGFR). In colorectal cancer (CRC), the balance between pro-angiogenic and anti-angiogenic factors is disturbed in favor of a pro-angiogenic outcome (angiogenic switch) early in the neoplastic progression of adenomas, thus, resulting in neovascularization and eventually in malignant tumor progression. Furthermore, angiogenesis plays an important role in tumor growth and the formation of metastases. Several angiogenic growth factors have been identified to be highly expressed during the progression and metastatic spread of CRC, but VEGFA is the predominant angiogenic cytokine and the most consistently expressed factor during the metastatic process. Agents targeting VEGF/VEGFR signaling have shown efficacy in the treatment of mCRC and are currently approved in this setting. In this review, we summarize the role of antiangiogenic tyrosine kinase inhibitors (TKIs) in the treatment of mCRC, focusing on regorafenib.*

CRC is the fourth most common tumor type in both sexes and the third most common cause of cancer death. More than 1.8 million new CRC cases and approximately 800,000 deaths occurred globally in 2018 (1, 2). Almost half of patients with resectable tumor at the time of initial diagnosis will eventually develop metastases, while one in four patients will be diagnosed with primary metastatic disease. For stage IV patients, survival rates at five years range from 5% to 15% (3, 4).

Initiation, progression and metastatic spread of CRC depend on various signaling pathways, the most prominent of these are the VEGF and the EGFR pathways (5-7). VEGF family proteins and their receptors (VEGFRs) play a central role in tumor angiogenesis, activating multiple signaling networks that result in endothelial cell growth, vessel formation, increased vascular permeability, tumor survival, proliferation and metastatic spread. Therefore, up-regulation of angiogenesis is a critical process for sustained tumor growth and is also of particular importance in the development of metastases (8-11). The angiogenic effects of the VEGF ligands are mediated by binding to cognate tyrosine kinase receptors (TKRs) on the cell surface (7-9), thus, causing their homo- and heterodimerization and activation through transphosphorylation. Phosphorylation is followed by the activation of a series of signaling pathways, such as RAS-RAF-MAPK, FAK-SRC, or AKT-mTOR (12).

In mCRC therapeutics, various agents have been used to inhibit angiogenesis, such as (a) monoclonal anti-VEGF antibodies that bind and neutralize VEGF; (b) a fusion soluble protein consisting of the ligand-binding domains of VEGFR-1 and VEGFR-2 that are fused to the Fc portion of human IgG1 and acting, therefore, as soluble "decoy" receptor; (c) monoclonal antibodies that target VEGFR; (d) cytotoxic agents that inhibit angiogenic chemokines; (f) peptibodies; and (g) orally available inhibitors that target several TKRs involved in both tumor growth and angiogenesis.

In this review article, we will focus on the role of TKIs and especially regorafenib in mCRC.

Regorafenib: Structure and Mechanism of Action

Regorafenib is a potent multi-kinase inhibitor that belongs to the group of biaryl urea chemicals and has activity against several protein kinases related to the angiogenic pathway

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(VEGFR-1/2/3, TIE2, PDGFR-α/β, and FGFR-1/2), the oncogenic pathway (KIT, RAF1, BRAF, and RET), the metastatic process, and the immunosuppressive activity of the tumor microenviroment (13-17). Regorafenib was discovered in a program aimed at optimizing the potency and other pharmacological properties of known urea class compounds, such as sorafenib, which is a successful prototype of diphenylurea derivatives. The only structural difference between regorafenib and sorafenib is that the former has a fluorine atom in the central phenyl ring. This modification of regorafenib results in a similar but distinct biochemical profile when compared with sorafenib (13, 17). *In vitro*, regorafenib inhibits various TKRs with 50% inhibitory concentration (IC_{50}) values ranging from 4.2 to 311 nM/l for angiogenic TKRs, from 1.5 to 7 nM/l for oncogenic TKRs, from 22 to 202 nM/l for stromal kinases and from 2.5 to 28 nM/l for intracellular signaling kinases (13, 17). Regorafenib is exclusively metabolized in the liver *via* cytochrome P3A4 and uridine diphosphate-glucuronosyltransferase 1A9, which increases the risk of drug-induced liver injury (17, 18).

Phase II and III Clinical Trials With Regorafenib Monotherapy

In the phase III CORRECT trial (19), patients with mCRC who had progressed after all approved standard therapies were randomized to receive best supportive care (BSC) plus 160 mg oral regorafenib or placebo, once every day for three weeks, followed by one week off treatment. All patients had received previous anti-VEGF treatment and 48% of them >3 prior lines of treatment in the metastatic setting. Median overall survival (OS) was 6.4 months in the regorafenib group *versus* 5.0 months in the placebo group [hazard ratio (HR)=0.77; p=0.0052]. Median progression-free survival (PFS) was 1.9 months in the regorafenib group *versus* 1.7 months in the placebo group (HR=0.49; p<0.0001). Clinical adverse events (AEs) of Grade ≥3 included hand-foot skin reaction (HFSR), *i.e.*, rash and numbness affecting the palms and soles (17%), fatigue (10%), hypertension (7%), diarrhea (7%), rash or desquamation (6%), oral mucositis (3%), and anorexia (3%). Laboratory abnormalities of Grade ≥3 included hypophosphatemia (4%), thrombocytopenia (4%), anemia (2%), hyperbilirubinemia (2%), and proteinuria (1%). A *post hoc* analysis that assessed the efficacy and safety profile of regorafenib in Japanese and non-Japanese subpopulations participating in the CORRECT trial did not show significant differences between the two groups (20). Based on the results of the CORRECT trial, regorafenib was approved in 2012 by the FDA as monotherapy for patients with mCRC who have been previously treated with, or who cannot be given, other available treatments, including fluoropyrimidine-based chemotherapy, an anti-VEGF therapy and an anti-EGFR therapy (21).

The double-blind, placebo-controlled, phase III CONCUR trial (22) was designed to evaluate the efficacy and safety of regorefenib in Asian patients from China, Hong Kong, South Korea, Taiwan, and Vietnam who had refractory mCRC. They were randomized in a 2:1 ratio to receive BSC plus regorafenib or placebo, exactly as in the CORRECT trial (19). Median OS (primary endpoint) was 8.8 months in the regorafenib group *versus* 6.3 months in the placebo group (HR=0.55; one-sided p=0.00016) and median PFS 3.2 months *versus* 1.7 months, respectively (HR=0.31; one-sided p<0.0001). The type and rate of clinical AEs of Grade ≥3 did not differ significantly from those described in the CORRECT trial (19) with HFSR being again the most frequent adverse event (16%). The *post hoc* subgroup analysis of Chinese patients (from mainland China, Taiwan, and Hong Kong), who were included in the CONCUR trial representing 84% of the overall population, showed that the TKI provided an OS and PFS benefit, compared to placebo, similar to that reported in CONCUR with no differences in toxicity and its management (23).

A Brazilian single-center, single-arm, phase IIb study enrolled patients who were antiangiogenic therapy-naïve (24). Almost half of them had received ≥4 prior lines of therapy on or after diagnosis of mCRC. Median PFS was 3.5 months, and median OS 7.4 months. Disease control rate (DCR) by RECIST criteria was 51% and metabolic response rate by EORTC criteria 41%. With the exception of a higher incidence of hypophosphatemia and hypertension, the safety profile of regorafenib was generally consistent with that previously reported in the randomized trials CORRECT (19, 20) and CONCUR (22, 23).

Finally, two phase II studies enrolled patients based on *KRAS* and/or *BRAF* status. In particular, the prematurely stopped for failing to accrue PREVIUM trial (25) did not demonstrate, in the population analyzed, clinical activity of regorafenib in *KRAS*- or *BRAF*-mutated mCRC with disease progression after first-line treatment with FOLFOXIRI plus bevacizumab. In the second study, the Japanese REVERCE trial (26), patients with *KRAS* exon 2 wild-type mCRC were randomized after failure of fluoropyrimidine, oxaliplatin, and irinotecan to receive sequential treatment with regorafenib followed by cetuximab with or without irinotecan (R-C arm), or the reverse sequence (C-R arm). Median OS was 17.4 months in the R-C arm and 11.6 months in the C-R arm (HR=0.61; p=0.0293), while the quality of life (QoL) scores throughout the treatment were not significantly different between the two arms. Mutations in *KRAS*, *NRAS*, *BRAF*, and *EGFR* and gene amplification of *HER2*, and *MET* were analyzed in circulating tumor DNA (ctDNA) extracted from patients' plasma. Oncogenic alterations were more common after R-C than after C-R sequence.

Observational Studies With Regorafenib Monotherapy in the Real-World Setting

Regorafenib has also been evaluated in four single-arm, open-label studies that were performed in real-world setting. The REBECCA cohort study was designed as part of a French compassionate use program (Autorisation Temporaire d'Utilisation, ATU) to assess survival, safety, and potential prognostic factors for regorafenib treatment in patients with mCRC refractory to standard treatments (27). Of 1178 patients included in the ATU program, 654 were fully analyzed. Median OS was 5.6 months and the 12-month survival rate was 22%. Independent prognostic factors with an unfavorable effect on survival were: poor performance status, time from initial diagnosis of mCRC to the start of regorafenib treatment <18 months, low initial regorafenib dose, >3 metastatic sites, presence of liver metastases, and *KRAS* mutations. Based on these variables, the authors constructed a prognostic model which categorized patients into three risk groups. Patients with low-, intermediate-, and high-risk score had a median OS of 9.2, 5.2, and 2.5 months, respectively. Eighty percent of patients experienced at least one regorafenib-related AE. In general, the activity and toxicity of regorafenib reported in REBECCA were similar to those observed in randomized trials.

The single-arm, phase IIIb CONSIGN trial (28) analyzed, across 25 countries, 2,864 patients with mCRC refractory to standard therapy who received regorafenib in an expanded access program prior to market authorization. The primary endpoint of the study was safety. Clinical drug-related AEs of Grade ≥3 were observed in 57% of patients, and included hypertension (15%), HFSR (14%), fatigue (13%), diarrhea (5%), maculopapular rash (3%), oral mucositis (2%), and anorexia (2%). Laboratory drug-related toxicities of Grade ≥3 included hypophosphatemia (5%), hyperbilirubinemia (5%), and elevated aspartate aminotransferase and alanine aminotransferase serum (3%) levels. Treatment-emergent AEs resulted in treatment discontinuation in 25% of patients, dose reduction in 46%, and treatment interruption or delay in 68%. Again, the frequency and rates of AEs were consistent with those reported in in the CORRECT (19, 20) and CONCUR (22, 23) trials. Median PFS of the entire cohort was 2.7 months. The subgroup with longer PFS tended to consist of a slightly higher proportion of patients with better performance status, absence of liver metastases and a longer interval from the time of diagnosis of metastatic disease as compared to the subgroup with shorter PFS. These findings are similar to those of the REBECCA study (27) described earlier.

The population of the international, prospective, observational CORRELATE study (29) consisted of approximately 1,000 patients with mCRC who had previously been treated with, or were not considered candidates for, other approved therapies and for whom the treating physician decided to treat them with regorafenib according to the local health authority approved label. Safety was the primary objective. The most common AEs of Grade ≥3 included fatigue (9%), HFSR (7%) and hypertension (6%). Dose reductions for AEs occurred in 24% of patients. Median OS and PFS were 7.7 months and 2.9 months, respectively. Finally, the recently published phase IIIb, REGARD study (30) that evaluated the safety and efficacy of TKI among Turkish patients with treatment-refractory disease showed similar toxicity profile and PFS (primary endpoints) to those reported in previous trials.

Retrospective Analyses Comparing Regorafenib With TAS-102

Sueda *et al*. (31), retrospectively analyzed a small number of mCRC patients whose disease had progressed after standard therapies and who were treated with either regorafenib or TAS-102, an oral formulation that combines trifluorothymidine (TFT) and the potent thymidine phosphorylase inhibitor tipiracil hydrochloride (TPI), in a molar ratio of 1:0.5 (32, 33). TAS-102 has successfully completed two randomized phase II/III studies (34, 35). In 2017, FDA approved TAS-102 as a third- or fourth-line treatment of mCRC, after chemotherapy and targeted therapeutics have failed (36).

The results of the Japanese study showed that both agents had comparable efficacy but different toxicity profile. In the regorafenib group, median PFS and OS were 3.0 and 5.8 months, respectively, and in the TAS-102 group, 2.1 and 6.3 months, respectively. It is worth noting, that the median OS was 11.5 months in patients initially receiving regorafenib and at disease progression TAS-102, but only 7.6 months in those receiving the reverse sequence. Another Japanese study that retrospectively analyzed a larger number of patients came to the same conclusions (37).

A third Japanese study (REGOTAS) (38) retrospectively analyzed a much larger number of patients than the other two Japanese studies reported earlier. Median OS was 7.9 months in the regorafenib group and 7.4 months in the TAS-102 group. The propensity score adjusted analysis showed that OS was similar between the two treatment groups (adjusted HR=0.96; 95%CI=0.78-1.18). Interestingly, in the subgroup analysis, regorafenib showed better survival outcomes in patients aged <65 years (HR=1.29; 95%CI=0.98-1.69), whereas TAS-102 in patients aged ≥65 years (HR=0.78; 95%CI=0.59-1.03).

Finally, a fourth retrospective Japanese study showed that patients that had previously received more systemic treatment lines, treated with regorafenib and were more likely to receive additional chemotherapy lines after disease progression on regorafenib compared to those treated with

TAS-102 (39). In this comparative study, median OS was 9.9 and 11.4 months in the regorafenib and TAS-102 group, respectively, while median PFS was 2.0 and 3.3 months, respectively (HR=0.52; p=0.00047). On the other hand, ORR and DCR did not differ. Median OS of patients receiving additional systemic therapies after disease progression was longer than that of patients without further treatment.

Dose-escalation Trials of Regorafenib

Despite the obvious survival benefits from the use of regorafenib in refractory mCRC, the toxicity of the drug and especially HFSR and fatigue create problems in its therapeutic application. In the CORRECT (19, 20) and CONCUR (22, 23) trials the standard dose of regorafenib was 160 mg, orally, once every day for three weeks, followed by one week off treatment. Data from clinical trials have shown that regorafenib-related AEs appear early after starting treatment, usually within the first cycle, and improve rather than worsen over time (19, 40). In clinical practice, physicians have usually adopted different dosing regimens or interval schedules to reduce toxicity. In this context, and in order to optimize the dosing strategy of regorafenib in patients with refractory mCRC, two phase II studies evaluated a dose-escalation strategy.

The randomized, multicenter, open-label, phase II study ReDOS, assessed the safety and activity of two regorafenib dosing schedules (41). Patients were randomly assigned into four groups with two different regorafenib dosing strategies and two clobetasol propionate cream usage plans. The steroid cream may help prevent HFSRs in patients receiving regorafenib. Dosing strategies included a dose-escalation strategy (initial dose of regorafenib 80 mg, once every day, with a weekly dose increase of 40 mg to the final dose of 160 mg, once every day, if no significant drug-related AEs occurred) and a standard-dose strategy (160 mg of regorafenib, once every day for three weeks, followed by one week off treatment). The primary endpoint, which was the proportion of patients in each group who completed two cycles of treatment and initiated the third cycle, was met, *i.e.*, significantly more patients in the dose-escalation group started cycle 3 than in the standard-dose group (one-sided p=0.043). The most common AEs of Grade ≥3 were fatigue (13% of patients in the dose-escalation group *versus* 18% in the standard-dose group), HFSR (15% *versus* 16%), abdominal pain (17% *versus* 6%), and hypertension (7% *versus* 15%).

In the single-arm, phase II RESET trial (42), 70 Japanese patients were treated with a lower starting dose of regorafenib (120 mg, once every day) and then the dosage was increased to 160 mg, once every day, on day 15 of the first cycle in patients who met dose escalation criteria, *i.e.*, they did not experience HFSR of any Grade and treatment-related AEs of Grade ≥2. Pharmacokinetics of total and unbound drug and its active metabolites were assessed. Only 6 patients (8.6%) achieved dose escalation to 160 mg, on day 15, as planned. DCR (primary endpoint) was 32.4%, which was below the threshold of the statistical hypothesis. Serum concentrations of total regorafenib in patients whose dose was increased to 160 mg were significantly lower than the relative serum concentrations in patients whose dose was not increased. Furthermore, non-bound serum concentrations of the sum of regorafenib and active metabolites were significantly correlated with the maximum Grade of regorafenib-related symptomatic AEs in the first cycle. In addition to the aforementioned dose escalation trials, another retrospective Japanese study examined the effectiveness of a reduced initial dose of regorafenib compared to the standard starting dose using a national database (43). Median OS was 12.6 months in the reduced dose group and 12.3 months in the standard dose group (p=0.41). As expected, most AEs occurred less frequently in the reduced dose group.

Regorafenib in Elderly Patients

Two phase II trials assessed the efficacy and safety of regorafenib in the elderly population. An Italian study evaluated an alternative schedule in patients ≥75 years old (44). They received regorafenib 160 mg, once every day for two weeks, followed by one week off treatment (2/1 schedule). The initial dose was reduced to 120 mg in patients considered vulnerable or with more than one comorbidities, and to 80 mg in patients ≥80 years old or with ECOG PS=2. DCR two months after treatment initiation (primary endpoint) was 52.2%. Median PFS was 4.8 months and median OS 8.9 months, respectively. Interestingly, AEs were uncommon, and the most frequent Grade 3 toxicities were HFSR (9%) and fatigue (9%). Another French, single-arm, phase II trial (FFCD 1404-REGOLD), evaluated regorafenib at the approved dose in patients ≥70 years old (45). The two-month DCR after treatment initiation (primary endpoint) was 31.4%. Median PFS and OS were 2.2 and 7.5 months, respectively. The median time to autonomy degradation and QoL degradation were 3.1 and 3.2 months, respectively. Treatment-related AEs of Grade ≥3 were observed in 83% of patients, in particular fatigue (45.2%), HFSR (19.0%), hypertension (21.4%), and diarrhea (7.1%). Both studies indicate that regorafenib can be given to elderly patients with similar efficacy compared with younger patients in previous studies. Dose reductions may result in a favorable toxicity profile without compromising antitumor activity, in terms of PFS and OC.

Regorafenib in Combination With Chemotherapy

Regorafenib plus multi-agent chemotherapy. A multicenter, phase Ib study explored whether the addition of regorafenib to the regimens FOLFOX or FOLFIRI could be feasible as

first- or second-line treatment of mCRC, in terms of safety and pharmacokinetic interactions of the various drug components of the combination. Among patients evaluated for response, the rates of partial response and disease stabilization were 18.4% and 68.4%, respectively. Median PFS was 116 days in the FOLFOX group, and 186.5 days in the FOLFIRI group. It should be noted that >50% of patients required a reduction in the dose of chemotherapy due to AEs and this could explain the relatively low clinical efficacy observed in this trial (46).

The international, multicenter, single-arm, open-label, phase II CORDIAL trial (47) investigated the addition of regorafenib to modified FOLFOX6 as first-line treatment of mCRC. The combination did not improve ORR over historical controls. Median OS was not reached, whereas median PFS was 8.5 months. Regorafenib plus modified FOLFOX6 did not appear to be associated with a significantly worse tolerability profile compared to modified FOLFOX6 alone.

The addition of regorafenib to FOLFIRI, as a second-line treatment, showed only a modest increase in PFS compared to FOLFIRI alone, in another phase II trial that randomized patients with disease progression after first-line chemotherapy with oxaliplatin and fluoropyrimidine in a 2:1 ratio to FOLFIRI plus regorafenib or FOLFIRI plus placebo (48). Median PFS was 6.1 months with FOLFIRI plus regorafenib *versus* 5.3 months with FOLFIRI plus placebo (HR=0.73; 95%CI=0.53-1.01; p=0.056), while no differences in OS were observed between the two arms (HR=1.01; 95%CI=0.71-1.44). Treatment-emergent AEs of Grade ≥3 with a >5% absolute increase from regorafenib included diarrhea, neutropenia, febrile neutropenia, hypophosphatemia, and hypertension.

In contrast to the findings of the two aforementioned prospective studies which did not show any particular benefit from the addition of regorafenib to first- or second-line chemotherapy, a retrospective cohort study from Taiwan (49) showed that the combination of regorafenib with chemotherapy (either single regimen 5-FU, irinotecan, oxaliplatin, or combination regimen FOLFIRI/FOLFOX), in the various treatment lines of mCRC, resulted in superior OS (20.9 months *versus* 10.3 months, p=0.015). In a more recent, prospective trial from the same country, patients with disease progression after all approved standard therapies were subjected to *UGT1A1* genotyping and received in the third- or fourth-line setting the combination of regorafenib and FOLFIRI with dose-escalated irinotecan (50). The overall DCR was 58.5%, whereas the median PFS and OS were 6.0 months and 12.0 months, respectively. Patients with wild-type *KRAS* had a significantly longer OS compared to those with *KRAS* mutations (14.4 *versus* 6.0 months; HR=0.40; p=0.014) but no significant difference was observed in PFS (9.0 *versus* 3.5 months; HR=0.57; p=0.117). Positive EGFR expression had an inverse correlation with PFS and OS. Moreover, left-sided tumors were associated with superior PFS and OS. The same research group is conducting a phase II study that randomizes patients in a 2:1 ratio to FOLFIRI (with irinotecan dose escalation according to *UGT1A1* genotyping) plus 120 mg regorafenib or to regorafenib alone (51).

Regorafenib plus TAS-102. The combination of regorafenib with TAS-102 is also interesting. The phase I trial REMETY (52) performed with a conventional 3+3 dose finding aimed to determine the recommended phase II dose of this combination and its efficacy in the third- or fourth-line of treatment. DCR after 8 weeks was 58.3%, remarkably better compared to historical data with regorafenib or TAS-102 alone. Furthermore, toxicities were consistent with the safety profile of each of the two agents alone.

Combination of Regorafenib With Immune Checkpoint Inhibitors

The phase Ib REGONIVO, EPOC1603 trial (53) assessed the safety and efficacy of regorafenib plus nivolumab for patients with metastatic gastric cancer and mCRC. It has been shown in experimental murine models of CRC that regorafenib reduces the number of tumor-associated macrophages (TAMs) (54), which have a tumor-promoting phenotype, primarily through suppression of T-cell mediated anti-tumor immune response (55). It has also been found in patients with gastric cancer that targeting VEGFR-2 reduces immunosuppressive regulatory T cells (Tregs) within the tumor microenvironment (56). Therefore, regorafenib is expected to have a similar effect since it is a VEGFR TKI. REGONIVO, EPOC1603 trial enrolled 25 patients with gastric cancer and 25 patients with CRC who had received ≥2 previous lines of chemotherapy, including anti-angiogenetic inhibitors in 96% of them. ORR was 44% in patients with gastric cancer and 36% in patients with CRC, while median PFS was 5.6 and 7.9 months, respectively. The combination had a manageable toxicity profile.

Selected ongoing phase I and II clinical trials investigating regorafenib in combination with other agents in mCRC are presented in Table I. Ongoing randomized trials are presented in Table II.

Systematic Reviews and Meta-analyses of Regorafenib Trials

The randomized phase III trials CORRECT (19) and CONCUR (22) showed that regorafenib when compared to placebo significantly increased PFS and OS with survival benefits of 1.4 and 2.5 months, respectively. A meta-analysis of 14 abstracts and 10 articles, demonstrated an even greater treatment effect on PFS (HR=0.40) and OS (HR=0.67) compared to placebo. These results were mainly supported

Table I. *Selected ongoing phase I and II clinical trials investigating regorafenib in combination with other agents in metastatic colorectal cancer.*

Study identifier	Type of study	Study population	Regimen/Treatment arms	Status
NCT03305913	Phase I (REMETY)	Third-line treatment for patients who had previously received at least one fluoropyrimidine-based chemotherapy, an anti-VEGF and, in case of *RAS* wt[a] tumors, an anti-EGFR treatment	Regorafenib plus TAS-102 (3+3 dose finding strategy)	Recruiting
NCT03712943	Phase I	Patients with pMMR[b]/MSS[c] disease that progressed through or become intolerant to fluoropyrimidine, irinotecan, oxaliplatin, and bevacizumab, and if *KRAS* wt, cetuximab or panitumumab containing therapies	Regorafenib plus Nivolumab	Active, not recruiting
NCT04362839	Phase I	Patients with pMMR/MSS disease that progressed within six months following the last administration of approved standard therapies which must include a fluoropyrimidine, oxaliplatin, irinotecan and anti-EGFR agent	Regorafenib orally, once every day for three weeks, followed by one week off treatment plus Nivolumab IV, every 2 weeks plus Ipilimumab IV, every 6 weeks	Recruiting
NCT03828799	Phase I/II (FOLFIRINOX-R)	First-line treatment in patients with *RAS* mutated mCRC	FOLFIRINOX plus Regorafenib	Recruiting
NCT03657641	Phase I/II	Patients who had failed or are intolerant of oxaliplatin, irinotecan, and 5-FU	Pembrolizumab IV over 30 minutes on day 1 plus Regorafenib orally, on days 1 to 14	Recruiting

[a]Wild-type; [b]proficient mismatch-repair; [c]microsatellite stable.

by the non-randomized studies. The most frequently reported AEs were HFSR (25%-86%), hypertension (11%-47%) and fatigue (2%-73%) (57). Another meta-analysis published in 2018 came to the same conclusions (58).

The first meta-analysis that assessed the efficacy and safety of regorafenib *versus* TAS-102 in mCRC (59) included the randomized trials CORRECT (19) and CONCUR (22) of regorafenib and the RECOURSE trial (60) of TAS-102. When compared with placebo, regorafenib demonstrated benefit for OS (HR=0.67; 95%CI=0.48-0.93) with TAS-102 showing a similar magnitude of benefit (HR=0.69; 95%CI=0.57-0.83) in direct comparison. Also, no differences were observed in PFS, ORR, and DCR. However, regorafenib was associated with more significant toxicity of any Grade (Risk Difference=0.31; 95%CI=0.25-0.38; p=0.001), especially HFSR and fatigue. On the other hand, regorafenib showed less hematologic toxicity. In the indirect comparison, no statistically significant differences were observed between regorafenib and TAS-102 in terms of OS (HR=0.96; 95%CI=0.57-1.66; p=0.91) or PFS (HR=0.85; 95%CI=0.40-1.81; p=0.67). Similar results were published by Sonbol *et al*. (61) in their meta-analysis of regorafenib and TAS-102, which included the following trials: CORRECT (19), CONCUR (22), ReDOS (41), RECOURSE (58), the double-blind, placebo-controlled, phase III trial TERRA of TAS-102 monotherapy in Asian patients (62), and a Japanese double-blind, randomized, placebo-controlled phase II trial of TAS-102 (63).

Finally, three meta-analyses compared regorafenib, TAS-102 and fruquintinib in refractory mCRC. All concluded that the three agents had similar OS but fruquintinib was superior, in terms of PFS, when compared with TAS-102. Furthermore, fruquintinib was associated with significantly increased risk for severe AEs compared with regorafenib and TAS-102 (64-66).

Other TKIs in mCRC

Sorafenib. Sorafenib is a multikinase inhibitor with activity against intracellular (CRAF, BRAF and mutant V600E BRAF) and cell surface kinases (KIT, FLT-3, VEGFR-1/2/3, RET, and PDGFR-β) (67-69). Sorafenib has been approved for the treatment of hepatocellular carcinoma, advanced renal cell carcinoma, refractory to radioactive iodine differentiated thyroid carcinoma, and FLT3-Internal Tandem Duplication (ITD) positive acute myeloid leukemia. In the RESPECT trial (70), patients with mCRC were randomized to receive as first-line treatment sorafenib or placebo, combined with mFOLFOX6. Median PFS and OS in the experimental and control arm, respectively, were 9.1 *versus* 8.7 months (HR=0.88; p=0.46), and 17.6 *versus* 18.1 months (HR=1.13; p=0.51), respectively. In addition, there were no differences in survival outcomes between the two treatment arms by *KRAS*, *BRAF* or *PIK3CA* status. The most common AEs of Grade ≥3 in the sorafenib and placebo arms were neutropenia (48% *versus* 22%), peripheral neuropathy (16%

versus 21%), and HFSR (20% *versus* 0%). The authors concluded that these results do not support the further development of sorafenib in combination with mFOLFOX6 in molecularly non selected patients with mCRC.

In another randomized phase II trial (NEXIRI 2-PRODIGE 27) (71), patients with *RAS* mutated mCRC, who had progressed after all approved standard therapies were randomized in 3 arms: NEXIRI (400 mg of oral sorafenib, twice daily, combined with irinotecan 120 mg/m^2 in cycle 1; doses were increased to 150 mg/m^2 in cycle 2 and 180 mg/m^2 in cycle 3 if patients had no diarrhea of Grade >1 and no other toxicity of Grade >2) *versus* irinotecan alone (180 mg/m^2) *versus* sorafenib alone, until disease progression or unacceptable toxicity, with cross-over to NEXIRI in the two monotherapy arms at disease progression. Median PFS was 3.7, 1.9, and 2.1 months in the NEXIRI, irinotecan, and sorafenib arm, respectively. It is worth noting, that patients with the *CCND1rs9344* A/A genotype were more likely to benefit.

Sunitinib. Sunitinib is another oral TKI with activity against VEGFR, PDGFR, KIT, RET, and FLT-3 (72, 73). Sunitinib has been approved for the treatment of unresectable or metastatic gastrointestinal stromal tumors (GISTs) after failure of imatinib treatment, advanced renal cell carcinoma, and pancreatic neuroendocrine tumors. In a phase II trial, Saltz *et al*. (74), treated patients with mCRC, after failure of standard therapy, with oral sunitinib 50 mg, once every day for four weeks, followed by two weeks off treatment (schedule 4/2). Sunitinib did not demonstrate a meaningful single-agent ORR in chemorefractory mCRC. However, the authors concluded that the mechanisms of action and the acceptable safety profile of this agent warrant further study in conjunction with standardized regimens for mCRC. In this context, an open-label phase I trial was conducted to evaluate the safety and pharmacokinetics of sunitinib in combination with FOLFIRI (75). Based on the promising results of this study, a double-blind, phase III study was conducted that randomized 768 patients with previously untreated mCRC to receive FOLFIRI and either sunitinib or placebo until disease progression. Median PFS for the sunitinib arm was 7.8 months *versus* 8.4 months for the placebo arm. In addition, treatment with sunitinib was associated with a higher rate of AEs of Grade ≥3 than FOLFIRI plus placebo. Therefore, the authors concluded that the combination of FOLFIRI with sutinib is not recommended for previously untreated mCRC (76). Relevant are the results of a phase II study that investigated the same combination as first-line treatment in patients with liver metastases (77).

Vatalanib. Vatalanib is an orally available TKI with activity against VEGFR-1/2/3, KIT, PDGFR and FMS (78). In a phase IB trial, FOLFOX4 was combined with vatalanib at escalating doses. Median PFS was 11.4 months (79). In another phase I/II study, vatalanib was combined with FOLFIRI as first-line treatment in patients with mCRC. Preliminary results suggested that the combination was safe, well tolerated, and had activity (80). Therefore, vatalanib was subsequently evaluated in two randomized phase III trials. In the first-line setting, 1,168 patients were randomly assigned to receive FOLFOX4 plus valatanib or placebo (81). Median PFS was 7.7 months with vatalanib *versus* 7.6 months with placebo (HR=0.88; p=0.118), while median OS was 21.4 *versus* 20.5 months (HR=1.08; p=0.260), respectively. In a *post hoc* subgroup analysis of patients with high serum LDH, a potential marker of hypoxia, PFS was 7.7 months with vatalanib *versus* 5.8 months with placebo (HR=0.67; p=0.009).

In the other phase III trial, patients with pretreated mCRC were randomly assigned to receive FOLFOX4 and either vatalanib or placebo (82). Median OS was 13.1 with vatalanib *versus* 11.9 months with placebo (HR=1.00; p=0.957), respectively. On the other hand, median PFS was longer with vatalanib than with placebo (5.6 *versus* 4.2 months, respectively; HR=0.83; p=0.013). Again, a *post hoc* analysis demonstrated improved PFS in patients with high LDH, regardless of performance status (HR=0.63; p<0.001). However, both phase III trials are considered negative studies, as their primary endpoints (PFS in the first and OS in the second) were not met.

Tivozanib. Tivozanib is a selective oral TKI with a long half-life and activity against VEGFR-1/2/3 (83). Tivozanib has been approved by EMA for the treatment of metastatic renal cell carcinoma. In a phase Ib study, patients with advanced gastrointestinal tumors were treated with tivozanib (0.5 mg, 1.0 mg, or 1.5 mg orally, once every day for three weeks, followed by one week off treatment) in combination with mFOLFOX6. Among 30 patients, 1 had an ongoing clinical complete response of more than 2.5 years, and 10 had a partial response, for an ORR of 37%. Another 11 patients experienced disease stabilization, lasting from 1.8 to 24.6 months. Furthermore, treatment appeared to be safe (84).
Based on these very encouraging results, an open-label, randomized phase II trial (BATON-CRC) (85) of tivozanib plus mFOLFOX6 *versus* bevacizumab plus mFOLFOX6 in treatment-naïve patients with mCRC was initiated. The combination of tivozanib and mFOLFOX6 was tolerable. Median PFS was 9.4 months for tivozanib plus mFOLFOX6 *versus* 10.7 months for bevacizumab plus mFOLFOX6 (HR=1.091; p=0.706). Also, tivozanib plus mFOLFOX6 resulted in ORR comparable with that of bevacizumab plus mFOLFOX6 (45.2% *versus* 43.2%, respectively). Of note, PFS in patients with low neuropilin-1 (NRP-1) was 17.9 months in the tivozanib arm *versus* 11.2 months in the bevacizumab arm (HR=0.38; unstratified p=0.0075). For patients with high NRP-1, no differences in PFS were observed between the two arms.

Table II. *Selected ongoing randomized phase II and phase IIII clinical trials investigating regorafenib in combination with other agents in metastatic colorectal cancer.*

Study identifier	Type of study	Study population	Regimen/Treatment arms	Status
NCT03880877	Randomized Phase II	Patients for whom the decision has been made per investigator's routine treatment practice to prescribe regorafenib as third-line (*RAS* mut) or fourth-line (*RAS* wt[a]) therapy	*Comparator arm:* Regorafenib 120 mg orally, once every day for three weeks, followed by one week off treatment *Experimental arm:* Regorafenib plus Irinotecan (180 mg/m^2 as a 120-min IV infusion for TA6/6 wt and TA6/7 *UGT1A1* genotypes or 120 mg/m^2 for TA7/7 *UGT1A1* genotype), followed by Leucovorin (400 mg/m^2 as a 120-min IV infusion), and 5-FU[b] (2,800 mg/m^2 IV infusion over a 46-hour period), repeated every 2 weeks (FOLFIRI[c])	Recruiting
NCT04008511	Phase Ib/ Randomized Phase II	Second-line treatment in patients with disease progression after first-line treatment with 5-FU and irinotecan	*Comparator arm:* Oxaliplatin 130 mg/m^2, IV on day 1, and Capecitabine 1,000 mg/m^2, bid orally for 14 days (XELOX) *Experimental arm:* Regorafenib MAD[d] orally, once every day for two weeks, followed by one week off treatment plus XELOX	Not yet recruiting
NCT01298570	Randomized Phase II	Second-line treatment for patients with disease progression during or within 6 months after first-line treatment with oxaliplatin plus 5-FU (with or without LV) or capecitabine with or without bevacizumab	*Arm A:* FOLFIRI plus Placebo *Arm B:* FOLFIRI plus Regorafenib 160 mg orally, once every day, days 4 to 10 and days 18 to 24, every four weeks	Active not recruiting
NCT04117945	Randomized Phase II (REVERCE II)	Patients with *KRAS, NRAS* and *BRAF* V600E wt mCRC previously treated with fluoropyrimidine, oxaliplatin and irinotecan	*Arm A:* Regorafenib orally, once every day for three weeks, followed by one week off treatment. Patients with disease progression may switch over to the other treatment regimen, per treating physician discretion. *Arm B:* Cetuximab or Panitumumab IV on days 1 and 15 with or without Irinotecan as determined by the study doctor. Patients with disease progression may switch over to the other treatment regimen, per treating physician discretion.	Recruiting
NCT03844620	Randomized Phase II	Patients with disease progression after ≥2 prior lines of treatment including 5-FU, oxaliplatin, irinotecan, bevacizumab, and if *KRAS* wt cetuximab or panitumumab	*Comparator arm:* Regorafenib orally, once every day for three weeks, followed by one week off treatment or TAS-102 orally, twice daily on days 1 to 5 and 8 to 12, every four weeks, as per SOCh, until disease progression or unacceptable toxicity *Experimental Arm:* Regorafenib or TAS-102. Patients will get ctDNA[g] testing and will continue treatment beyond the first cycle depending on ctDNA results until disease progression or unacceptable toxicity.	Recruiting

Table II. *Continued*

Table II. *Continued*

Study identifier	Type of study	Study population	Regimen/Treatment arms	Status
NCT03992456	Randomized Phase II (PULSE)	Patients with KRAS wt disease that progressed to a fluoropyrimidine, oxaliplatin, irinotecan, and an anti-VEGF monoclonal antibody or an anti-PD-1 monoclonal antibody if tumor has deficient MMR[f] or is MSI-H[h]	*Comparator arm:* TAS-102 orally on days 1 to 5 and 8 to 12, or Regorafenib orally, once every day for three weeks, followed by one week off treatment (at the discretion of the treating physician) *Experimental arm:* Panitumumab IV on days 1 and 15, every four weeks	Recruiting
NCT03829462	Phase III (NEXT-REGIRI)	Patients with disease progression during or within 3 months following the last administration of all approved standard therapies, which must include a fluoro-pyrimidine, oxaliplatin, irinotecan, anti-VEGF therapy and an anti-EGFR therapy (for *RAS* wt tumors)	*Comparator arm:* Regorafenib 160 mg orally, once every day for three weeks, followed by one week off treatment *Experimental arm:* Irinotecan 180 mg/m^2 at day1 of each cycle plus Regorafenib 160 mg orally, once every day, days 2 to 8	Recruiting

[a]Wild-type; [b]5-fluorouracil; [c]after every 2 cycles of each different dose of irinotecan, if adverse events are Grade <2 dose will be escalated by 30 mg/m^2 with an estimated maximal dose of 260 mg/m^2 for TA6/6 *UGT1A1* genotype TA6, 240 mg/m^2 for TA6/7, and 180 mg/m^2 for TA7/7; [d]maximum administered dose; [e]standard-of-care; [f]circulating tumor; [g]mismatch-repair; [h]microsatellite instability-high.

Vandetanib. Vandetanib is an oral TKI that targets VEGFR-1/2/3, EGFR and RET (86). It has been approved for the treatment of advanced/metastatic medullary thyroid cancer. In a phase I study, vandetanib was tested in combination with cetuximab and irinotecan as second-line treatment in patients with mCRC (87). Seven percent of patients had a partial response, 59% stable disease and 34% progressed. Median PFS was 3.6 months and median OS 10.5 months. Toxicities were quite manageable with diarrhea of Grade ≥3 being the common treatment-related AE (30%). The observed effectiveness raised interest in further evaluating of this combination.

In another phase I study, vandetanib was combined with capecitabine and oxaliplatin, with and without bevacizumab, in the first-line setting (88). ORR was 46%, while the time to disease progression ranged from 2 to 14 months. Oral vandetanib at doses of 100 mg and 300 mg, daily, in combination with capecitabine and oxaliplatin was well tolerated. However, the addition of bevacizumab caused diarrhea of Grade 3.

Nintedanib. Nintedanib is a small molecule with activity against receptor tyrosine and non-receptor tyrosine kinases, such as PDGFR-α/β, FGFR-1/2/3, VEGFR-1/2/3, FLT-3, Lck, Lyn and Src (89). Nintedanib has been approved for the treatment of patients with interstitial lung disease associated with systemic sclerosis or scleroderma, and in combination with docetaxel for the treatment of patients with advanced/metastatic adenocarcinoma of the lung. The combination of nintedanib with chemotherapy was compared with the combination of bevacizumab with chemotherapy, in a randomized phase I/II study, as first-line treatment in patients with mCRC. In the phase II part, patients were randomized in a 2:1 ratio to receive nintedanib plus mFOLFOX6 or bevacizumab plus mFOLFOX6. PFS rate at 9 months was 62.1% in the nintedanib arm *versus* 70.2% in bevacizumab arm, while confirmed ORRs were 63.5% and 56.1%, respectively. Furthermore, the safety profile of nintedanib in combination with mFOLFOX6 was manageable (90).

The LUME-Colon 1 trial (91) had the same design as the CORRECT (19, 20) and CONCUR (22, 23) trials. More specifically, this double-blind, placebo-controlled, phase III study assessed the efficacy and safety of oral nintedanib (200 mg twice daily) plus BSC *versus* placebo plus BSC in patients with mCRC who had progressed after all approved standard therapies. Median PFS was 1.5 months with nintedanib plus BSC *versus* 1.4 months with placebo plus BSC (HR=0.58; $p<0.0001$), but this increase by 42% did not result in improved OS.

Fruquintinib. Fruquintinib (HMPL-013) is a highly selective TKI with activity against VEGFR-1/2/3 (92). A phase Ib open-label study was followed by another phase II, randomized, placebo-controlled trial that evaluated the efficacy and safety of fruquintinib (5 mg orally, once every day for three weeks, followed by one week off treatment) plus BSC *versus* placebo

plus BSC in patients with mCRC who had received at least two lines of prior therapies. In the randomized phase II trial, median PFS was 4.73 months with fruquintinib plus BSC *versus* only 0.99 months with placebo plus BSC (HR=0.30; $p<0.001$). Patients who received fruquintinib had a longer median OS (7.72 *versus* 5.52 months), however, the difference was not statistically significant (93).

These encouraging results led to a phase III study (FRESCO-2) (94) with patients enrolled from 28 centers in China, who met similar inclusion criteria, and who were randomized in the same way and received exactly the same treatment as the patients of the aforementioned phase II study. Median PFS was significantly increased with fruquintinib (3.71 *versus* 1.84 months; HR=0.26; $p<0.001$), but more importantly, OS (primary endpoint) was also significantly increased with the TKI (9.3 months in the fruquintinib arm *versus* 6.57 months in the placebo arm; HR=0.65; $p<0.001$). Statistically significant benefits were also seen with fruquintinib in the other secondary endpoints, such as ORR and DCR. The most frequent fruquintinib-related AEs of Grade ≥3 included hypertension (21.2%), HFSR (10.8%), proteinuria (3.2%), diarrhea (2.9%), and thrombocytopenia (2.5%). Based on the results of this trial, FDA granted fast track designation to fruquintinib for mCRC patients previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy and -if RAS wild-type- an anti-EGFR therapy (95).

Famitinib. Famitinib (SHR1020) is a TKI that targets VEGFR-2/3, KIT and PDGFR-α/β, RET, FLT-1 and FLT-3 (96). A multicenter, phase II clinical trial randomized in a 2:1 ratio patients with mCRC whose disease progressed after all available standard therapies to receive either famitinib or placebo. Median PFS was 2.8 in the famitinib arm *versus* 1.5 months in the placebo arm (HR=0.60; $p=0.004$). No significant differences in OS were observed between the two arms. The most frequent AEs of Grade ≥3 included hypertension, HFSR, thrombocytopenia, and neutropenia (97).

Axitinib. Axitinib, an indazole derivative, is an oral, highly selective inhibitor of VEGFR-1/2/3 (98). In a multicenter, open-label, randomized phase 2 trial, patients with previously untreated mCRC were randomized in a 1:1:1 ratio to receive axitinib (5 mg, orally, twice a day), bevacizumab (5 mg/kg, intravenously, every 2 weeks), or axitinib (5 mg, orally, twice a day) plus bevacizumab (2 mg/kg, intravenously, every 2 weeks), each in combination with FOLFOX6. The addition of axitinib only or axitinib plus bevacizumab to chemotherapy did not improve ORR, PFS or OS compared to bevacizumab plus FOLFOX (99). Another phase II trial, randomized patients after failure of first-line therapy to chemotherapy (mFOLFOX-6 or FOLFIRI) plus either axitinib or bevacizumab. There were no significant differences in survival outcomes between the two treatment arms. AEs of Grade ≥3 were more common with axitinib (100).

A recently published randomized phase II trial, evaluated the efficacy and safety of maintenance therapy with axitinib *versus* placebo following induction therapy. More specifically, patients with mCRC who had not progressed after 6 to 8 months of first-line chemotherapy were randomized to receive maintenance therapy with axitinib or placebo. Median PFS was 4.96 months in the axitinib arm *versus* 3.16 months in the placebo arm (HR=0.46; $p=0.0116$). Although median OS was also longer in the axitinib arm, this difference did not reach statistical significance (27.61 *versus* 19.99 months; HR=0.68; $p=0.3279$). Maintenance therapy had a good safety profile (101).

Apatinib. Apatinib (YN968D1) is a potent inhibitor of VEGFR-2, PDGFR-β, KIT and SRC (102). In a Chinese pilot study, apatinib was active as a third-line treatment of refractory mCRC with a manageable toxicity profile (103).

Conclusion

Numerous antiangiogenic TKIs have been tested in mCRC. Most of the clinical trials have evaluated regorafenib alone or in combination with other agents in the various treatment lines. Regorafenib is indicated for the treatment of patients with mCRC who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if *KRAS* wild-type, an anti-EGFR therapy. In practice, the place of regorafenib is in the third- or fourth-line of treatment, where TAS-102 and more recently fruquintinib represent another option. Regorafenib and TAS-102 do not differ in terms of DCR, PFS and OS but have different toxicity profiles, which may guide the treatment choice. For better tolerance of regorafenib, the dose-escalation strategy has yielded acceptable results. The combination of regorafenib with other agents, especially immune checkpoint inhibitors, is also of interest. Among the other antiangiogenic TKIs, fruquintinib has given encouraging results.

Conflicts of Interest

MP has nothing to disclose. CAP has received speaker honoraria and honoraria for consultancy in advisory boards from Novartis, Pfizer, AstraZeneca, Genesis, MSD, Amgen, Merck and Roche and research grants from BMS and Roche.

Authors' Contributions

MP had the initial conception for the review, drafted the original manuscript, made substantial contributions to acquisition and interpretation of the literature, and has given final approval of the version to be published.

CAP drafted the original manuscript, made substantial contributions to acquisition and interpretation of the literature, and has given final approval of the version to be published.

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