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ADIS DRUG EVALUATION

Regorafenib: A Review of Its Use in Previously Treated Patients with Progressive Metastatic Colorectal Cancer

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Abstract Regorafenib (Stivarga®) is an inhibitor of multiple protein kinases, including those involved in oncogenesis, tumour angiogenesis and maintenance of the tumour microenvironment. The drug is approved as monotherapy for the treatment of metastatic colorectal cancer (mCRC) in patients who have previously received all standard systemic anticancer treatments (US, EU and Canada) or in patients with unresectable, advanced or recurrent colorectal cancer (Japan). In the randomized, controlled COloRectal cancer treated with REgorafenib or plaCebo after failure of standard Therapy (CORRECT) trial, regorafenib 160 mg once daily for the first 3 weeks of each 4-week cycle plus best supportive care (BSC) was associated with a significantly longer median overall survival than placebo plus BSC in patients with previously treated, progressive mCRC. The drug was also associated with significantly longer progression-free survival and better disease control rates than placebo, although objective response rates were similar in both treatment groups. Regorafenib did not appear to compromise health-related quality of life over the study duration and had a generally acceptable tolerability profile. The introduction of regorafenib expands the currently limited range of effective treatment options in patients with previously treated, progressive mCRC.

Regorafenib in previously treated patients with progressive metastatic colorectal cancer (mCRC): a summary

A small molecule inhibitor of multiple protein kinases, including VEGFR-1, -2 and -3, TIE2, FGFR, PDGFR, KIT, RET, RAF-1 and BRAF

Prolongs median overall survival and progression-free survival without compromising health-related quality of life in previously treated patients with progressive mCRC

Most common treatment-related grade 3 adverse events associated with regorafenib are hand-foot skin reactions, fatigue, hypertension, diarrhoea, rash or desquamation, hypophosphataemia, anorexia, oral mucositis and thrombocytopenia

1 Introduction

Globally, colorectal cancer (CRC) is the second leading cause of cancer in females and the third leading cause in males, with an estimated >1.2 million new cases and >600,000 deaths occurring in 2008 [1]. Although improvements in the awareness, early detection and treatment of CRC have resulted in decreasing or stabilizing CRC incidence and CRC-related mortality rates in many Western countries, rapid increases in the incidence of CRC are being observed in a number of countries with historically low incidence rates (e.g. Spain, Japan, Czech Republic), reflecting such factors as changes in dietary patterns, obesity rates and an increased prevalence of smoking [1]. CRC-related mortality is also continuing to increase in countries with limited resources and healthcare

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infrastructure (e.g. Central and South America, Eastern Europe). Thus, the disease is a large global public health concern [2].

In the US, the overall 5-year survival rate in patients with CRC is 64 %, increasing to 90 % in those with localized disease and declining to 12 % (or even 5–8 % [3]) in those with distant metastases at diagnosis [4]. Approximately 50–60 % of patients with CRC will develop metastatic disease, with the liver being the most common site of metastatic involvement [5]. Although curative surgery is possible in patients with resectable liver metastases, 80–90 % of patients who develop metastatic CRC (mCRC) have unresectable metastatic liver disease [5].

Combination chemotherapy (e.g. folinic acid, fluorouracil and either irinotecan [FOLFIRI] or oxaliplatin [FOLFOX]) with or without targeted agents (e.g. the anti-VEGF monoclonal antibody bevacizumab [6] or the anti- EGFR monoclonal antibodies cetuximab [7] and panitumumab [8] [see Table 1 for acronym definitions]) is the mainstay of first- or second-line treatment for mCRC [5, 9]. However, drug-related adverse events and drug resistance may limit the potential of such treatments [2]. In many patients, all of these treatment options have been exhausted in earlier lines of therapy, leaving very limited options for third-line treatment [2]. This is particularly problematic in patients with mutant KRAS tumours (30–40 % of CRC tumours have KRAS mutations [10]), in whom anti-EGFR monoclonal antibodies are ineffective [2]. Hence, there is continued need for novel targeted agents [2], and those targeting multiple signalling pathways are of particular interest in the wider field of novel anticancer agents [11–13].

Regorafenib (Stivarga®) is a multikinase inhibitor (Sect. 2.1) that is approved for the treatment of mCRC in patients who have previously received all standard systemic anticancer treatments (or who are not candidates for such treatments [14]) in the US [15], EU [14] and Canada [16], and in patients with unresectable, advanced or recurrent CRC in Japan [17] (Sect. 6).

Regorafenib is now included in the US National Comprehensive Cancer Network guidelines for colon [5] or rectal [9] cancer as an additional line of therapy for patients with metastatic disease who are refractory to chemotherapy. The recommendations are to use regorafenib in the third-line setting in patients with mutant KRAS tumours and in the third- or fourth-line setting in those with wild-type KRAS tumours [5]. Similarly, regorafenib is also included in the European Society for Medical Oncology guidelines for CRC as a third or fourth-line option in patients with advanced disease [18]. This article reviews the therapeutic efficacy and tolerability of regorafenib in previously treated patients with progressive mCRC, as well as data pertaining to the pharmacology of regorafenib that are relevant to this indication.

Table 1 Acronym definitions

Acronym	Definition
AKT	v-akt murine thymoma viral oncogene homologue 1
BRAF	v-raf murine sarcoma viral oncogene homologue B1
$BRAF^{V600E}$	V600E-mutant BRAF
DDR2	Discoidin domain receptor tyrosine kinase 2
EGFR	Epidermal growth factor receptor
EphA2	Ephrin type-A receptor 2
ERK	Extracellular signal-regulated kinases
FGF(R)	Fibroblast growth factor (receptor)
KIT	v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homologue
KRAS	v-Ki-ras2 Kirsten rat sarcoma viral oncogene homologue
MEK	Mitogen-activated protein kinase kinase
MET	Met proto-oncogene
p38-α	Mitogen-activated protein kinase 11
p38-β	Mitogen-activated protein kinase 14
PDGF(R)	Platelet-derived growth factor (receptor)
PIK3CA	Phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha
PKC	Protein kinase C
PTK5	Protein tyrosine kinase-5
RAF-1	v-raf-1 murine leukaemia viral oncogene homologue 1
RET	ret ("rearranged during transfection") proto-oncogene
TIE2	Tyrosine kinase with immunoglobulin-like and epidermal growth factor-like domains 2
VEGF(R)	Vascular endothelial growth factor (receptor)

2 Pharmacodynamic Properties

2.1 Mechanism of Action

Regorafenib is a small molecule inhibitor of multiple protein kinases, including those involved in the pathological processes of oncogenesis (KIT, RET, RAF-1, BRAF, $BRAF^{V600E}$), tumour angiogenesis (VEGFR-1, -2 and -3, TIE2) and maintenance of the tumour microenvironment (PDGFR, FGFR) [see Table 1 for acronym definitions] [15, 16, 19]. The chemical structure of regorafenib (Fig. 1) is similar to that of sorafenib, with the substitution of a hydrogen atom and a fourth fluorine atom in the central aromatic ring, giving regorafenib a broader spectrum of action than sorafenib [20].

In biochemical assays, regorafenib potently inhibited VEGFR-1, -2 and -3, TIE2, FGFR1, PDGFR-β, KIT, RET, RAF-1, BRAF and $BRAF^{V600E}$ at nanomolar concentrations (concentration of regorafenib required to inhibit activity by 50 % [IC_{50}] 1.5–311 nmol/L) [21]. Results of cellular kinase phosphorylation assays were generally consistent with those of the biochemical assays, except for

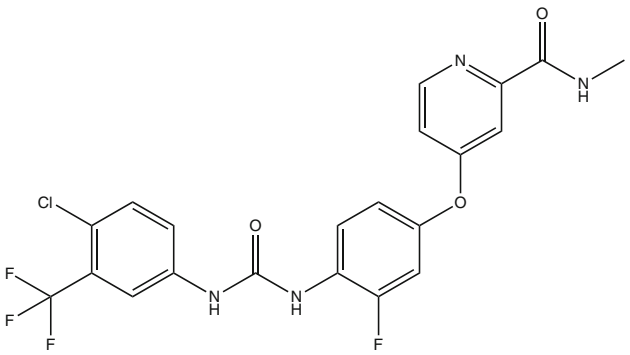

Fig. 1 Chemical structure of regorafenib

regorafenib-induced inhibition of TIE2, which was ≈10-fold weaker in the biochemical than cellular assays [21].

Regorafenib also inhibited other kinases in vitro, including DDR2, EphA2, PTK5, p38-α and p38-β (IC_{50} values <100 nmol/L) [21]. Some kinases, including EGFR or PKC family kinases, MEK, MET, ERK-1 or -2 and AKT, were not inhibited by regorafenib, even at high concentrations [21].

Proliferation of FGF2-, PDGF subunit B- and, particularly, $VEGF_{165}$-stimulated vascular cell lines was also inhibited by regorafenib in vitro, with IC_{50} values of 2.6–146 nmol/L [21]. The effect of regorafenib on the proliferation of different tumour cell lines varied, with cell lines known to express activated oncogenic mutants of KIT (human gastrointestinal stromal tumour [GIST] cell line) or RET (human medullary thyroid carcinoma cell line) receptors being potently inhibited (IC_{50} 34–45 nmol/L) and colon cancer cell lines (IC_{50} 967–3,269 nmol/L) and melanoma, breast or liver cancer cell lines (IC_{50} 401–900 nmol/L) being less so.

In another in vitro study, regorafenib demonstrated antitumour activity (in terms of reduced cell proliferation) in 19 of 25 human CRC cell lines (IC_{50} 1–10 μmol/L), with no correlation seen between the antitumour activity of the drug and the presence or absence of KRAS or BRAF mutations (abstract presentation) [22].

2.2 Angiogenesis and Antitumour Effects

Regorafenib inhibited tumour perfusion in patients with advanced solid tumours [23] or CRC [24] in phase I trials, as measured with various techniques including the dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) initial area under the concentration-time curve over the first 60 s after injection of the contrast agent ($iAUC_{60}$). For example, in the CRC study, the median $iAUC_{60}$ ratio ($iAUC_{60}$ at time point vs. $iAUC_{60}$ at baseline) was 0.803, 0.661 and 0.507 on day 2 of regorafenib treatment cycle 1, day 21 of cycle 1 and day 21 of cycle 2, respectively [24]. No apparent association was seen between $iAUC_{60}$ and progression-free survival (PFS).

The antiangiogenic effects of regorafenib were also demonstrated in animal xenograft models of various cancer types [21, 25]. At clinically effective dosages (considered to be 10–30 mg/kg once daily [21]), the drug significantly ($p < 0.05$ vs. control) reduced tumour microvessel area in murine xenograft models of CRC [21, 25], including a model of highly aggressive, orthotopic colon cancer [25]. In the latter study, there was no significant difference between the regorafenib-receiving and control groups in terms of the number of mature vessels detected in the tumours, but the drug was associated with a significant ($p < 0.05$ vs. control) decrease in the numbers of VEGFR-2- or TIE2-positive vessels. Furthermore, in tracer kinetic analyses of longitudinal DCE-MRI measurements, regorafenib was associated with a significantly ($p < 0.05$) lower relative distribution volume of contrast agent than control, as indicated by lower signal-time curve amplitudes. There was no significant difference between the regorafenib-receiving and control groups in blood vessel permeability, as assessed using the exchange rate constant k_{ep} [25].

A qualitative reduction in tumour vascularity was also observed with a 30-mg/kg once-daily dosage of regorafenib in a murine xenograft model of breast cancer, with areas of reduced endothelial cell-marker staining also exhibiting tumour necrosis [21]. In this model, decreased tumour cell proliferation contributed to regorafenib-associated inhibition of tumour growth, as indicated by a qualitative reduction in the area of cell proliferation-marker staining seen in regorafenib-receiving compared with control animals [21]. In addition, a qualitative reduction in staining for activated pERK1/2 in regorafenib-receiving compared with control animals demonstrated that the drug inhibits the RAF/MEK/ERK signalling cascade in vivo.

Oral regorafenib dose-dependently inhibited tumour growth in various murine xenografts models, including models of CRC [21, 25], breast cancer and renal cell carcinoma [21]. For example, in one of the CRC models, tumour growth was effectively inhibited at once-daily dosages of 10–100 mg/kg, with ≈75 % of tumour growth inhibition being reached on day 14 after receiving a clinically-effective dosage of 10 mg/kg once daily [21]. In all dosage groups, slow tumour regrowth was seen 9 days after drug discontinuation.

In the other colon cancer model, regorafenib was associated with significant ($p < 0.01$ vs. control) reductions in tumour growth from day 3 of treatment, and with an 18.4-fold higher rate of apoptosis on day 10 ($p < 0.01$ vs. control) [25]. The drug also appeared to inhibit metastatic dissemination of colon cancer cells to the liver, with no liver metastases seen in any of the regorafenib-receiving

animals; in contrast, liver metastases were seen in five of six control animals [25].

Infiltration of tumour-associated macrophages was identified as a possible mechanism behind the failure of antiangiogenic therapy in murine cancer models, although the significance of this in human cancer remains unknown [26]. In a murine xenograft model of highly aggressive, orthotopic colon cancer, regorafenib 30 mg/kg once daily was associated with a significant decrease (≈4-fold; $p < 0.001$ vs. control) in macrophage infiltration after 10 days' treatment [25].

Preliminary results of an exploratory biomarker subanalysis of data from a phase III study (Sect. 4) indicated that none of the 15 potential protein biomarkers assessed (including many involved in angiogenesis) were significant predictors of regorafenib efficacy after correction for multiple testing (abstract presentation) [27].

2.3 Cardiovascular Effects

Drug-related hypertension is an adverse event associated with all antiangiogenic drugs, including regorafenib (Sect. 5.1), and may predict better clinical outcomes [28]. In a small ($n = 32$) study in patients with GIST, 63 % of whom developed hypertension, regorafenib rapidly and reversibly suppressed vasodilatory nitric oxide (NO) and stimulated vasoconstrictive endothelin-1 (ET-1) [28]. Thus, plasma levels of NO and ET-1 could potentially be used as biomarkers to predict a favourable response to treatment [28]. However, further studies are required [28].

The effect of regorafenib 160 mg once daily on cardiovascular safety parameters, including corrected QT (QTc) interval and left-ventricular ejection fraction, is being investigated in an ongoing dedicated cardiovascular safety study in patients with solid tumours [29]. Results of an interim analysis in 25 patients reported in the US FDA assessment report for regorafenib indicated that regorafenib had a minimal effect on QTc intervals at the time when maximum plasma concentrations (C_{max}) were expected to occur (t_{max}) [19]. At regorafenib t_{max}, the mean change from baseline in QTc (corrected using Fridericia's formula [QTcF]) interval was 2 ms; no patients had a QTcF value >500 ms. Thus, even with the most conservative evaluation, the observed maximal median change in QTc interval was not thought likely to be clinically significant [19].

Additional data from this same interim analysis of the cardiovascular safety study reported in the Canadian manufacturer's prescribing information demonstrated that regorafenib was associated with a statistically significant (p value not reported) decrease in heart rate from baseline at about 4–10 h after dose administration on day 21 of treatment [16]. The maximum mean decrease in heart rate from baseline was 8.2 beats per min.

3 Pharmacokinetic Properties

3.1 Absorption and Distribution

In a phase I dose-escalation study in patients with advanced solid tumours ($n = 53$) [Sect. 4], regorafenib systemic exposure at steady-state increased dose-proportionally at oral doses of up to 60 mg, but less than dose-proportionally at doses >60 mg, with the latter possibly reflecting limited solubility of the drug in gastrointestinal fluids [23]. For the M-2 and M-5 metabolites of regorafenib (Sect. 3.2), greater than proportional increases in exposure at steady state were observed with lower (<160 mg) regorafenib doses, although better dose proportionality was observed with higher (≥160 mg) doses.

Regorafenib mean C_{max} was 2.5 μg/mL, mean area under the plasma concentration-time curve (AUC) was 70.4 μg·h/mL and median t_{max} was 4 h in patients with advanced solid tumours receiving a single oral dose of regorafenib 160 mg [15]. At steady state, mean C_{max} was 3.9 μg/mL, mean AUC over a 24-h dosing interval (AUC_{24}) was 58.3 μg·h/mL and median t_{max} was 5 h [23]. The coefficient of variation of AUC and C_{max} values was 35–44 % [15].

Administration of a single oral dose of regorafenib 160 mg with a high-fat meal versus under fasting conditions increased the mean regorafenib AUC by 48 % in 24 healthy volunteers, and decreased the mean AUC of the M-2 and M-5 metabolites (Sect. 3.2) of regorafenib by 20 and 51 % [15, 16]. Administration of regorafenib with a low-fat meal (as opposed to under fasting conditions) increased the mean regorafenib, M-2 and M-5 AUC by 36, 40 and 23 %, respectively. Thus, it is recommended that regorafenib is administered with a low-fat meal (Sect. 6) [14–16].

Regorafenib enters the enterohepatic circulation and, thus, demonstrates multiple plasma concentration peaks over a 24-h dosing interval [14–16]. The drug is highly bound (99.5 %) to human plasma proteins [14–16], and has a mean apparent volume of distribution at steady state of 88 L [16].

3.2 Metabolism and Elimination

Regorafenib is primarily metabolized in the liver by the cytochrome P450 (CYP) isoenzyme CYP3A4 and by UDP-glucuronosyltransferase (UGT)-1A9 [14–16]. The drug has two main circulating metabolites, M-2 (N-oxide metabolite) and M-5 (N-oxide and *N*-desmethyl metabolite) and six minor metabolites [14, 16]. Both major metabolites have similar in vitro pharmacological activity and steady-state concentrations to the parent drug, and are also highly (≥99.8 %) plasma protein bound [14–16].

In patients with advanced solid tumours, the mean elimination half-life ($t_{1/2}$) of regorafenib after a single 160-mg dose was 28 h, and that of the M-2 and M-5 metabolites was 25 and 51 h [15]. At steady state, the mean regorafenib $t_{1/2}$ was 22 h [23].

Regorafenib is primarily excreted in the faeces and, to a lesser extent, the urine [14–16]. After administration of a radiolabelled dose of regorafenib 120 mg as an oral solution, ≈ 71 % of the dose was excreted in the faeces (47 % as parent drug and 24 % as metabolites) and 19 % in the urine (17 % as glucuronides) within 12 days of administration [15].

3.3 Special Patient Populations

Although the mean systemic exposure of regorafenib and its metabolites was numerically lower in Japanese patients ($n = 15$) with advanced solid tumours (e.g. mean regorafenib C_{max} was ≈2-fold lower after a single 160-mg dose) than previously observed in European patients (Sect. 3.1), the inter-individual variability was large [30]. Thus, no dosage adjustments were thought necessary in Japanese patients on the basis of these results [17, 30] (Sect. 6).

The presence of mild or moderate hepatic impairment did not appear to alter the pharmacokinetics of regorafenib, M-2 or M-5 [15]. No clinically significant differences in mean regorafenib, M-2 or M-5 exposure were observed between regorafenib-receiving patients with mild (Child-Pugh class A; $n = 14$) or moderate (Child-Pugh class B; $n = 4$) hepatic impairment in a study of hepatocellular carcinoma and those with normal hepatic function ($n = 10$) in a study of solid tumours. Thus, no dosage adjustments are thought necessary in patients with mild [14–17] or moderate [15, 17] hepatic impairment, although such patients should be monitored closely for adverse events throughout treatment because of the potential for regorafenib-associated hepatic adverse events (Sect. 5.3). The pharmacokinetics of regorafenib have not been evaluated in patients with severe hepatic impairment (Child-Pugh class C), and the use of regorafenib in such patients is not recommended [14–16].

Regorafenib pharmacokinetics were not affected by the presence of mild renal impairment, with no clinically relevant differences in mean regorafenib, M-2 and M-5 systemic exposure being observed between regorafenib-receiving patients with mild renal impairment (creatinine clearance [CL_{CR}] 60–89 mL/min) [$n = 10$] and those with normal renal function ($n = 18$) when administered at a dosage of 160 mg once daily for 21 days [15]. Thus, no adjustments to the dosage of regorafenib are required in patients with mild renal impairment [14–16]. Only limited data pertaining to the pharmacokinetics of regorafenib in patients with moderate renal impairment (CL_{CR} 30–59 mL/min) are available [14–17]; however, based on these limited data, no dose adjustment is thought necessary in such patients in the EU [14]. The pharmacokinetics of the drug in patients with severe renal impairment or end-stage renal disease have not been studied [14–17]. The US Center for Drug Evaluation and Research (CDER) has requested a multiple dose study to be performed as a post-marketing requirement to determine the appropriate dosage of regorafenib in patients with severe renal impairment [19].

3.4 Drug–Drug Interactions

In vitro studies demonstrated that regorafenib is a competitive inhibitor of CYP3A4, CYP2C8, CYP2C9, CYP2B6 and CYP2C19, M-2 is an inhibitor of CYP3A4, CYP2C8, CYP2C9 and CYP2D6 and M-5 an inhibitor of CYP2C8; based on in vitro data, the drug is not expected to induce CYP3A4, CYP1A2, CYP2B6 or CYP2C19 [15]. Regorafenib and its metabolites also inhibited UGT1A9 and UGT1A1 in vitro, and regorafenib inhibited the transporters P-glycoprotein and breast cancer resistance protein.

Mean regorafenib AUC was increased by ≈33 % and mean M-2 and M-5 AUC was decreased by 94 and 93 % when regorafenib was coadministered with the strong CYP3A4 inhibitor ketoconazole [16]. Thus, concomitant use of regorafenib with strong CYP3A4 inhibitors (e.g. clarithromycin, grapefruit juice, itraconazole, ketoconazole, telithromycin) should be avoided [14–16].

Coadministration of regorafenib with the strong CYP3A4 inducer rifampicin (rifampin) decreased the mean regorafenib AUC by 50 % and increased the mean M-5 AUC by 264 % in 22 healthy volunteers, although no effect on mean M-2 AUC was observed [15]. Thus, concomitant use of regorafenib with strong CYP3A4 inducers (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital and *Hypericum perforatum* [St John's wort]) should also be avoided [14–16].

Pharmacokinetic data obtained from a clinical probe substrate study indicated that coadministration of regorafenib with probe substrates of CYP2C8 (rosiglitazone), CYP2C9 (S-warfarin), CYP2C19 (omeprazole) or CYP3A4 (midazolam) was unlikely to result in a clinically meaningful drug–drug interaction [14, 16].

Concomitant use of regorafenib with FOLFIRI or FOLFOX increased mean irinotecan AUC by 28 % and mean SN-38 (an active metabolite of irinotecan) AUC by 44 % in patients ($n = 45$) with CRC, but had no clinically relevant effect on the pharmacokinetics of fluorouracil or oxaliplatin [31].

Antibacterials affecting gut flora may interfere with enterohepatic circulation [14, 16]. Thus, because regorafenib and its metabolites undergo enterohepatic

circulation, regorafenib exposure may be affected by coadministration with antibacterials [14, 16]. The clinical relevance of this is not yet known, although it is possible that the efficacy of regorafenib may be decreased as a result [14].

Regorafenib exposure may also be affected by coadministration with bile salt-sequestering agents (e.g. cholestyramine and cholestagel), because these agents may interact with regorafenib, resulting in the formation of insoluble complexes which may impact upon the drug's absorption [14]. Although the clinical relevance of this potential drug–drug interaction is not yet known, it is possible that the efficacy of regorafenib may be decreased as a result.

4 Therapeutic Efficacy

This section focuses on the efficacy of regorafenib monotherapy in patients with mCRC and disease progression after receiving treatment with all locally approved standard systemic anticancer therapies, as evaluated in the randomized, double-blind, multinational, phase III COloRectal cancer treated with REgorafenib or plaCebo after failure of standard Therapy (CORRECT) trial [32]. Key patient baseline characteristics and trial design details are shown in Table 2.

The first clinical evidence of antitumour activity in patients with CRC was demonstrated in a phase I dose-escalation study in 53 previously treated patients with advanced solid tumours who received oral regorafenib 10–220 mg once daily for the first 3 weeks of each 4-week cycle [23]. Based on results of the dose-escalation phase of the trial, the study was extended to focus on patients with mCRC [24]. All patients in the extension cohort received regorafenib 160 mg once daily [24], which was determined to be the recommended dosage for further study in the dose-escalation phase [23]. In an analysis of data from patients with mCRC participating in the dose-escalation ($n = 15$) and/or extension ($n = 23$) phases of the trial, of which 27 patients were evaluable for response, one patient had a confirmed partial response and 19 patients had stable disease, leading to a disease control rate of 74 % [24]. The remaining 7 evaluable patients had progressive disease. A total of 13 patients had tumour shrinkage (of any percentage) at any time during the study. Median PFS was 107 days and 13 patients had PFS >100 days at data cutoff. The phase III CORRECT trial was conducted on the basis of these favourable results [32].

4.1 The CORRECT Trial

Patients (median age of 61 years) participating in the CORRECT trial were randomized 2:1 to receive best supportive care plus oral regorafenib 160 mg or placebo once daily for the first 3 weeks of each 4-week cycle [32]. Treatment was to continue until disease progression, death, occurrence of unacceptable toxicity, withdrawal of patient consent or other patient- or physician-related reasons. Baseline characteristics were similar between the

Table 2 Key patient characteristics and trial design details of the CORRECT trial [32]

	Regorafenib ($n = 505$)	Placebo ($n = 255$)
Selected pt characteristics at baseline by treatment group:		
ECOG performance status (0/1) [% of pts]	52/48	57/43
KRAS mutation[a] (yes/no/unknown) [% of pts]	54/41/5	62/37/2
No. of previous systemic anticancer therapies (1–2/3/≥4) [% of pts]	27/25/49	25/28/47
Mean EORTC QLQ-C30 score	62.6	64.7
Mean EQ-5D index score	0.73	0.74
Mean EQ-5D VAS score	65.4	65.8
Key inclusion criteria:		
Male or female aged ≥18 years; histological or cytological documentation of colon or rectal adenocarcinoma; received all standard systemic anticancer therapies, including fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab and cetuximab or panitumumab (if KRAS wild type), if locally approved; progression during or within 3 months of last dose of standard therapy or discontinued standard therapy because of unacceptable toxicity; ECOG performance status ≤1; life expectancy ≥3 months; adequate bone marrow, liver and renal function		
Key exclusion criteria:		
History of other cancer (except curatively treated cervical cancer in situ, non-melanoma skin cancer and superficial bladder tumours) within previous 5 years; previously received regorafenib; history of other serious or uncontrolled medical disorder; unresolved toxicity >grade 1 attributed to any prior therapy/procedure (except alopecia or oxaliplatin-induced neurotoxicity of ≤grade 2)		

ECOG Eastern Cooperative Oncology Group, *EORTC QLQ-C30* European Organization for Research and Treatment of Cancer general health status and quality-of-life questionnaire-C30, *EQ-5D* EuroQol five dimension, *pt(s)* patient(s), *VAS* visual analogue scale

[a] Based on historical data collected at study entry

regorafenib and placebo arms, with the exception of the percentage of patients with KRAS mutations (based on historical data collected at study entry), which was numerically lower in the regorafenib than placebo arms (Table 2). The primary endpoint was median overall survival (OS).

Two formal interim analyses of OS data were conducted during the CORRECT trial, with the study to be stopped for proven efficacy at the second interim analysis if the one-sided *p* value for the hazard ratio (HR) [regorafenib vs. placebo] of median OS was ≤0.009279 (which roughly correlates with an HR of ≤0.7864) [32]. Unless otherwise specified, data reviewed here are those from this second interim analysis, which was conducted after 432 deaths had occurred. At this timepoint, the mean duration of treatment was 2.8 months in the regorafenib arm and 1.8 months in the placebo arm. Regorafenib-receiving patients received 78.9 % of the planned dose (mean daily dose 147.1 mg) whereas placebo-receiving patients received 90.1 % of the planned dose (mean daily dose 159.2 mg) [32]. The mean number of treatment cycles completed in the regorafenib arm was 3.3 cycles (data not reported for the placebo arm), and 16 % of regorafenib and 3 % of placebo recipients received ≥6 cycles of treatment [19].

At the second interim analysis, oral regorafenib 160 mg once daily was associated with significantly ($p = 0.0052$) longer median OS than placebo in previously treated patients with progressive mCRC (HR 0.77; 95 % confidence interval [CI] 0.64–0.94) [Table 3] [32]. Because the *p* value was less than the prespecified limit for proven efficacy of ≤0.009279, the primary endpoint was considered to be met and the study was unblinded, with four patients in the placebo group switching over into the regorafenib group at this time [32]. More recent OS data obtained from an analysis conducted after 566 deaths support these results, with the median OS being 6.4 months in the regorafenib arm and 5.0 months in the placebo arm (HR 0.79; 95 % CI 0.66–0.94; $p = 0.0038$) [abstract presentation] [33]. OS rates in the latter analysis were also consistent with those seen at the second interim analysis (Table 3), being 52.2 % in the regorafenib group and 43.1 % in the placebo group at 6 months and 24.1 and 17 % at 12 months [33].

The efficacy of regorafenib in previously treated patients with progressive mCRC was also demonstrated by other study endpoints in the second interim analysis, including median PFS (HR 0.49; 95 % CI 0.42–0.58) and disease control rates, which were both significantly better in regorafenib than placebo recipients (Table 3) [32]. However, no statistically significant difference was seen between the regorafenib and placebo arms in the objective response rate (ORR) [Table 3], which was comprised entirely of partial responses (five regorafenib recipients vs. one placebo recipient), with no patients in either treatment arm having a complete response [32].

Table 3 Efficacy of oral regorafenib in previously treated patients with progressive metastatic colorectal cancer. Results of the second preplanned interim analysis of the phase III CORRECT trial [32]. *P* values are given where available

Parameter[a]	Regorafenib ($n = 505$[b])	Placebo ($n = 255$[b])
Median OS (months)[c]	6.4*	5.0
OS rate (% of pts)		
3 months	80.3	72.7
6 months	52.5	43.5
9 months	38.2	30.8
12 months	24.3	24.0
Median PFS (months)	1.9**	1.7
ORR (% of pts)	1.0	0.4
Disease control rate (% of pts)	41**	15
Median duration of stable disease (months)	2.0	1.7

ORR objective response rate, *OS* overall survival, *PFS* progression-free survival, *pts* patients, * $p = 0.0052$, ** $p < 0.0001$ vs. placebo

[a] OS was defined as the time from randomization until death from any cause, PFS as the time from randomization until the first radiological or clinical observation of disease progression or death, ORR as the proportion of pts with a complete or partial response, and disease control rate as the proportion of pts with a complete or partial response or stable disease; tumour response and progression were defined using Response Evaluation Criteria in Solid Tumours version 1.1

[b] Intent-to-treat population

[c] Primary endpoint

4.1.1 Subgroup Analyses

Prespecified analyses of median OS in subgroups of patients (e.g. based on patient demographics, disease variables, KRAS mutation status, Eastern Cooperative Oncology Group performance status and previous number and type of anticancer regimens) suggested that the HRs (but not all the 95 % CIs) favoured regorafenib over placebo across most groups [32]. However, it should be noted that the CORRECT trial was not powered to detect OS benefit in patient subgroups.

In patients stratified according to the primary site of disease, regorafenib appeared to have a greater OS benefit versus placebo in patients ($n = 495$) with disease in the colon (HR 0.70; 95 % CI 0.56–0.89) than in those ($n = 220$) with disease in the rectum (HR 0.95; 95 % CI 0.63–1.44), while no significant between-group difference was observed in patients ($n = 44$) with disease in both the colon and rectum (HR 1.09; 95 % CI 0.44–2.70) [32], which may be because of the smaller number of patients in the latter subgroup.

In addition, a post-hoc exploratory biomarker subanalysis (using BEAMing technology) suggested that the treatment effect of regorafenib was consistent across subgroups of patients stratified according to baseline KRAS or PIK3CA mutation status, with no significant subgroup-by-treatment interaction being observed for the primary endpoint of median OS (abstract presentation) [34]. Subgroup analyses based on BRAF mutation status were not performed because of the low number (1.5 %) of mutant BRAF tumour samples.

4.1.2 Health-Related Quality of Life

Regorafenib did not appear to compromise health-related quality of life over the study duration, as demonstrated by mean European Organization for Research and Treatment of Cancer general health status and quality-of-life questionnaire-C30 scores, which were similar between regorafenib and placebo recipients at the second interim analysis (48.9 vs. 51.9 points) [32]. Mean EuroQol five dimension index (0.59 vs. 0.59 points) and visual analogue scale (55.5 vs. 57.3 points) scores at this time point were also similar in both treatment groups, indicating that regorafenib also did not have a detrimental effect on health status over the course of the study. Baseline scores for each of these scales are shown in Table 2.

5 Tolerability

This section focuses on the tolerability of regorafenib 160 mg once daily in previously treated patients with progressive mCRC, as evaluated in the pivotal phase III CORRECT trial (discussed in Sect. 4). Unless otherwise specified, results discussed here are from the CORRECT safety analysis ($n = 500$ regorafenib and 253 placebo recipients in safety population), which included adverse events occurring during treatment or within 30 days of permanent study drug discontinuation [19, 32].

5.1 General Tolerability Profile

The tolerability profile of regorafenib was generally acceptable in previously treated patients with progressive mCRC [19, 32]. Treatment-related adverse events occurred in 93 % of regorafenib and 61 % of placebo recipients [32]. The most frequently occurring treatment-related adverse events of any grade associated with regorafenib were fatigue (47 % of regorafenib vs. 28 % of placebo recipients) and hand-foot skin reactions (47 vs. 8 %) [Fig. 2a]. Most adverse events occurred during cycles 1 or 2 of treatment [32].

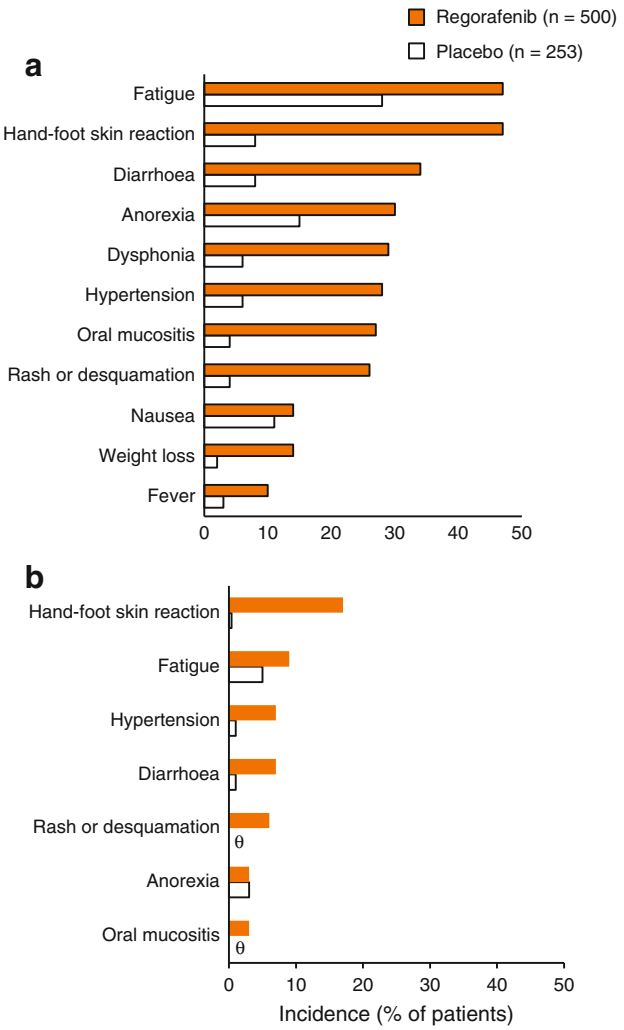

Fig. 2 Tolerability of regorafenib in previously treated patients with progressive metastatic colorectal disease. The most common treatment-related adverse events (excluding laboratory abnormalities) of **a** any grade (incidence ≥10 %) or **b** grade 3 severity (incidence ≥3 %) occurring in either treatment arm in the CORRECT trial [32]. θ indicates an incidence of 0 %

Aside from the incidence of grade ≥3 diarrhoea, which remained reasonably constant over time, the incidence of grade ≥3 hand-foot skin reactions, fatigue, hypertension or rash/desquamation generally peaked during cycle 1 of treatment and then decreased to lower and more stable incidence rates with later treatment cycles (abstract presentation) [35]. Thus, the study investigators recommended close monitoring for adverse events early in regorafenib treatment, with appropriate management measures taken, such as dosage modification [35].

Treatment-related grade 3 adverse events occurred in 51 % of regorafenib and 12 % of placebo recipients, with the most frequently occurring being hand-foot skin reactions (17 % of regorafenib vs. 0.4 % of placebo recipients), fatigue (9 vs. 5 %), hypertension (7 vs. 1 %), diarrhoea

(7 vs. 1 %) and rash or desquamation (6 vs. 0 %) [Fig. 2b] [32]. A total of 17 treatment-related grade 4 adverse events occurred in regorafenib recipients and included two cases of fatigue and one case of diarrhoea.

Adverse events leading to dosage interruptions (occurring in 61 % of regorafenib vs. 22 % of placebo recipients) or dosage reductions (38 vs. 3 %) were most commonly caused by hand-foot skin reactions and diarrhoea, and treatment-related adverse events leading to permanent study drug discontinuation (8.2 vs. 1.2 %) were most commonly caused by dermatological adverse events [19].

Serious adverse events occurred in 44 % of regorafenib and 40 % of placebo recipients [19, 32], and the nature of events were considered to reflect the disease being treated [19]. General health deterioration (7 % of regorafenib vs. 10 % of placebo recipients), pyrexia (3 vs. 0.4 %) and abdominal pain (2.4 vs. 1 %) were the most frequently occurring serious adverse events in the regorafenib group [19]. All other serious adverse events occurred at an incidence of $\leq$2 % in either treatment arm [19].

A total of 17 deaths were considered not to be associated with disease progression, 11 of which occurred in the regorafenib arm and included two cases of pneumonia and one case each of upper gastrointestinal haemorrhage, rectal and vaginal haemorrhage, pulmonary haemorrhage, cardiac arrest, general physical health deterioration, intestinal obstruction, cerebrovascular accident, sudden death and death of unknown cause [19].

5.2 Laboratory Abnormalities

The most frequently occurring treatment-related laboratory abnormalities of any grade were thrombocytopenia (13 % of regorafenib vs. 2 % of placebo recipients), hyperbilirubinaemia (9 vs. 2 %), proteinuria (7 vs. 2 %), anaemia (7 vs. 2 %) and hypophosphataemia (5 vs. 0.4 %) [32]. Grade 3 laboratory abnormalities included hypophosphataemia (4 % of regorafenib vs. 0.4 % of placebo recipients), thrombocytopenia (3 vs. 0.4 %), anaemia (2 vs. 0 %), hyperbilirubinaemia (2 vs. 1 %) and proteinuria (1 vs. 0.4 %), and grade 4 abnormalities included anaemia and thrombocytopaenia (0.4 and 0.2 vs. 0 %) [32].

Regorafenib was associated with an increased incidence of liver function test abnormalities, with numerically more regorafenib than placebo recipients having increased alkaline phosphatase (77 vs. 67 % of patients), AST (65 vs. 46 %), ALT (45 vs. 30 %) or bilirubin (45 vs. 17 %) levels of any grade [19]. Increases in AST or ALT of >3× the upper limit of normal (ULN) occurred in 6 % of regorafenib and 1 % of placebo recipients without liver metastasis and in 17 and 16 % of those with liver metastasis, and increases in bilirubin of >2× the ULN occurred in 6 % of regorafenib and 1 % of placebo recipients without liver metastasis and in 22 and 14 % of those with liver metastasis [19].

Regorafenib was also associated with a higher incidence of electrolyte (e.g. hypocalcaemia, hyponatraemia and hypokalaemia) and metabolic (e.g. increases in lipase and amylase levels) abnormalities than placebo [14, 16] and a numerically higher incidence of hypothyroidism (4.2 vs. 0.4 % of patients) [16].

5.3 Specific Adverse Events

Both the US [15], EU [14] and Canadian [16] manufacturer's prescribing information state that severe, fatal drug-induced liver injury occurred in 0.3 % of regorafenib recipients across all clinical trials. Because of this, the US manufacturer's prescribing information includes a boxed warning stating that severe and sometimes fatal hepatotoxicity has occurred with regorafenib in clinical trials [15]. Consequently, treatment with regorafenib requires monitoring of liver function, with dosage modifications or drug discontinuation as necessary (see local prescribing information for further details) [14–17].

Haemorrhagic adverse events of any grade occurred in numerically more regorafenib than placebo recipients (21.4 vs. 7.5 % of patients), with most ($\approx$90 %) being grade 1 or 2 in severity [19]. Epistaxis, haematuria and anal or rectal haemorrhage accounted for $\approx$70 % of all haemorrhagic adverse events [19]. Four fatal haemorrhagic adverse events occurred in the regorafenib arm, and included the three events described in Sect. 5.1 and one episode of gastrointestinal haemorrhage that was considered to be related to disease progression [19].

Regorafenib was associated with a numerically higher incidence of dermatological adverse events compared with placebo (72 vs. 24 % of patients), including hand-foot skin reactions (Sect. 5.1), rash (22 vs. 3 %), dry skin (9 vs. 3 %) and alopecia (8 vs. 2 %) [19]. Serious dermatological adverse events included erythema multiforme (0.2 % of regorafenib vs. 0 % of placebo recipients) and Stevens Johnson syndrome (0.2 vs. 0 %). Across all regorafenib clinical trials (n = 1,200), toxic epidermal necrolysis occurred in 0.17 % of regorafenib recipients [15].

Regorafenib was associated with a numerically higher incidence of myocardial ischaemia and myocardial infarction than placebo (1.2 vs. 0.4 % of patients) [15, 16, 19].

Gastrointestinal fistula and perforation are known class effects of anti-VEGF agents [19]. Across all regorafenib clinical trials, the incidence of gastrointestinal fistula or perforation was 0.6 % and included four fatal events [15].

6 Dosage and Administration

In the US [15], EU [14] and Canada [16], regorafenib is approved for the treatment of mCRC in patients who have previously received (or are not candidates for [14]) treatment with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF agent, and, if the tumour is KRAS wild type, an anti-EGFR agent. In Japan, the drug is approved for the treatment of unresectable, advanced or recurrent CRC [17]; the Japanese manufacturer's prescribing information specifies that the efficacy and safety of regorafenib as first- or second-line therapy in patients with CRC has not been established, and indicates that the drug should be used in patients with a similar treatment history to those included in the CORRECT trial (Sect. 4) [17].

The recommended dosage of regorafenib is 160 mg administered orally once daily for the first 3 weeks of each 4-week treatment cycle [14–17]. The drug should be administered at the same time each day, with a low-fat breakfast (in the US) [15] or after a light, low-fat (low-calorie [16]) meal (in the EU [14] and Canada [16]) [Sect. 3.1]. Japanese recommendations are to avoid administration of regorafenib under fasting conditions or after a high-fat meal [17]. Treatment should be continued until disease progression (or as long as a benefit is observed [14, 16]) or the occurrence of unacceptable toxicity [14–16].

On the basis of the tolerability profile of regorafenib (Sect. 5), monitoring of certain clinical parameters, including liver function [14–17], blood pressure [14–17], thyroid function [17] and/or other metabolic parameters and electrolytes [14, 16], is recommended. Blood count and/or coagulation parameters should be monitored in patients with conditions that may predispose them to bleeding [14] or in those receiving concomitant anticoagulant treatment (e.g. with warfarin) [14–16].

The drug should be permanently discontinued in patients with severe or life-threatening bleeding, gastrointestinal fistula or perforation, reversible posterior leukoencephalopathy syndrome [14–17], wound dehiscence [15, 16] or hypertensive crisis [14, 16, 17]. The drug should also be permanently discontinued in patients who are unable to tolerate an 80-mg dose of the drug, in patients with levels of AST or ALT of >20× ULN or of AST or ALT >3× ULN and of bilirubin >2× ULN, in patients with a reoccurrence of AST or ALT levels of >5× ULN despite dose reduction to 120 mg [14–16] and in patients with any grade 4 adverse event, although the drug may be restarted in this latter group of patients if the potential benefits of treatment are thought to outweigh the risks [15, 16].

Permanent discontinuation or dosage interruptions/reductions may also be required in those developing dermatological adverse events, liver function test abnormalities, hypertension, new or acute cardiac ischaemia or infarction [14–17] or metabolic or electrolyte abnormalities [14, 16]; for most of these, the course of action is determined by the severity and persistence of the adverse event [14–17]. In addition, because wound healing impairment is a class effect of anti-VEGF agents, regorafenib should be stopped (≥2 weeks [15, 16]) before scheduled surgery and restarted at the physician's discretion after wound healing has occurred [14–16].

In Canada, it is recommended that regorafenib is used with caution in patients with a low baseline heart rate (<60 beats per min), a history of certain cardiac diseases, including various conduction disorders and in those receiving concomitant medications known to decrease the heart rate [16]. Regorafenib is not recommended for use in patients with inadequately controlled blood pressure [14–16], and patients with a history of ischaemic heart disease should be monitored closely throughout treatment [14, 16]. See Sect. 3.3 for recommendations regarding the use of regorafenib in patients with a history of hepatic impairment.

Local prescribing information should be consulted for detailed information regarding potential drug interactions, use in special patient populations, monitoring requirements, dosage modifications, warnings and precautions.

7 Regorafenib in Previously Treated Patients with Progressive Metastatic Colorectal Cancer: Current Status

Limited options are available for third-line (or subsequent lines of) treatment of mCRC, particularly in those patients with mutant KRAS tumours [2]. Regorafenib is a multikinase inhibitor that is approved as monotherapy for the treatment of mCRC in patients who have previously received all standard systemic anticancer treatments in the EU [14], US [15] and Canada [16], and in patients with unresectable, advanced or recurrent CRC in Japan [17] (Sect. 6). In the US, the drug is also approved for use in patients with locally advanced, unresectable or metastatic GIST who have previously received imatinib and sunitinib [15]; it is also approved for use in patients with GIST who have progressed after prior systemic anticancer therapy in Japan [36] (discussion of this indication is beyond the scope of this review). The efficacy of regorafenib as first-line treatment for mCRC in combination with FOLFOX (modified FOLFOX 6) [37] or as second-line treatment for mCRC in combination with FOLFIRI [38] is currently being evaluated in phase II trials.

In the randomized, controlled CORRECT trial, regorafenib 160 mg once daily for the first 3 weeks of each 4-week cycle plus best supportive care (mean duration of

treatment 2.8 months) was associated with significantly longer median OS than placebo plus best supportive care (mean duration of treatment 1.8 months) in previously treated patients with progressive mCRC (Sect. 4.1). The drug also had a favourable effect on other endpoints, including median PFS and disease control rates (Sect. 4.1). No complete tumour responses were observed, and the ORR did not significantly differ between the regorafenib and placebo groups (Sect. 4.1). Regorafenib did not appear to compromise health-related quality of life over the study duration (Sect. 4.1.2).

Fatigue and hand-foot skin reactions were the most frequently occurring treatment-related adverse events of any grade in regorafenib recipients (Sect. 5.1). Hand-foot skin reactions were also the most frequently occurring treatment-related adverse event of grade 3 severity in regorafenib recipients, and the most common adverse event causing dosage modifications or study discontinuations (Sect. 5.1). Approaches to the prevention and/or management of multikinase inhibitor-associated hand-foot skin reactions include patient education, regular physician follow-up, control of hyperkeratosis (including removal of calluses), cushioning of hands and feet (e.g. with orthotic devices, thick cotton socks and gloves) and use of creams to moisturize and exfoliate the skin; dosage modifications (or permanent drug discontinuation) may be required for more severe hand-foot skin reactions [39–41]. Regorafenib may also have the potential to induce hepatotoxicity (Sect. 5.3). An open-label phase III trial further evaluating the safety of regorafenib in previously treated patients with progressive mCRC is ongoing [42]. In conclusion, the introduction of regorafenib expands the currently limited range of effective treatment options in previously treated patients with progressive mCRC.

Data selection sources: Medical literature (including published and unpublished data) on regorafenib was identified by searching databases including MEDLINE (from 1946) and EMBASE (from 1996) [searches last updated 26 September 2013], bibliographies from published literature, clinical trial registries/databases and websites. Additional information was also requested from the company developing the drug.
Search terms: Regorafenib, colorectal cancer, colorectal neoplasms.
Study selection: Studies in patients with metastatic colorectal cancer who received regorafenib. When available, large, well designed, comparative trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

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