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ADIS DRUG EVALUATION

Regorafenib: A Review in Metastatic Colorectal Cancer

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Abstract
Regorafenib (Stivarga®) is an oral small-molecule multiple kinase inhibitor. It is indicated worldwide for patients with metastatic colorectal cancer (mCRC). In the EU and USA it is indicated for patients with mCRC who have been previously treated with, or are not considered candidates for available therapies, including fluoropyrimidine-based chemotherapy, an anti-VEGF therapy and, if *RAS* wild-type, an anti-EGFR therapy. In Japan, it is indicated for the treatment of unresectable, advanced/recurrent CRC. The addition of regorafenib to best supportive care prolonged median overall survival (OS; by up to 2.5 months) and progression-free survival (PFS; by up to 1.5 months) relative to the addition of placebo in double-blind phase 3 studies (CORRECT and CONCUR) in patients with mCRC who had progressed after failure of standard therapy. Health-related quality of life was not adversely affected with regorafenib relative to placebo. A large open-label phase 3 study (CONSIGN) and several large real-world studies supported the efficacy of regorafenib in this setting. Regorafenib had a generally manageable tolerability profile, which was consistent with the profile of a typical small-molecule multiple kinase inhibitor. Treatment-related adverse events (AEs), mostly of mild or moderate severity, were reported in the majority of patients receiving regorafenib, with dermatological toxicities and liver enzyme elevations among the most common AEs. Although identification of biomarkers/parameters predicting efficacy outcomes with regorafenib will help to individualize therapy, current evidence indicates that regorafenib is a valuable treatment option for patients with refractory mCRC who have a very poor prognosis.

Regorafenib: clinical considerations in mCRC

When added to best supportive care, regorafenib prolongs OS and PFS in patients with mCRC who have progressed on previous standard therapy

Does not adversely affect health-related quality of life relative to best supportive care

Most common AEs include dermatological toxicities (e.g. hand-foot skin reaction, rash), liver enzyme elevations, gastrointestinal disorders (e.g. constipation, diarrhoea, mucositis) and hypertension

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1 Introduction

Colorectal cancer (CRC) is one of most common cancers diagnosed worldwide, accounting for an estimated 1.36 million new cases and 694,000 deaths in 2012 [1]. Treatment outcomes for patients with metastatic CRC (mCRC) have improved in recent years, particularly in the last decade, although which changes in the treatment and management strategies resulted in these improvements are unclear [2]. Patients with mCRC today have a median overall survival (OS) of ≈ 30 months [2]. Current treatment guidelines recommend a 'continuum of care' approach to disease management [2–4], with the choice of systemic therapy based on tumour- and disease-related characteristics (e.g. metastases limited to liver and/or lung, prognostic molecular or biochemical markers), patient-related factors (e.g. age, comorbidity, performance status) and treatment-related factors (e.g. toxicity, quality of life) [2]. The standard of care for unresectable, mCRC has been fluoropyrimidine-based therapy with or without anti-VEGF (e.g. bevacizumab, aflibercept, ramucirumab) or anti-EGFR (e.g. cetuximab, panitumumab) targeted therapy. In patients who are refractory to these therapies or for whom standard therapies are inappropriate, regorafenib

monotherapy or trifluridine/tipiracil (TAS-102) therapy are recommended [2–4]. Regorafenib (Stivarga®) is an oral small-molecule, multiple kinase inhibitor approved for use worldwide in this setting, including in the EU [5], USA [6] and Japan [7] (see Sect. 4 for indication details). Its pharmacological properties, efficacy and tolerability have been reviewed previously [8]. This article provides an update on the efficacy and tolerability of regorafenib, with its key pharmacological properties summarized in Table 1.

2 Therapeutic Efficacy of Regorafenib

2.1 Phase 3 Studies

The efficacy of regorafenib was assessed in two randomized, double-blind, multinational, phase 3 studies, CORRECT ($n=760$) [16] and CONCUR ($n=204$) [17], in patients with mCRC who had progressed after failure of standard therapy. The majority (78%) of patients in CORRECT were white (14% were Asian patients, mostly Japanese) [16, 18], while CONCUR required only Asian patients be enrolled and those included were largely (>90%) East Asian from China, Hong Kong, South Korea, Taiwan and Vietnam [5, 17].

In both studies, eligible patients were ≥18 years of age and had histologically or cytologically confirmed adenocarcinoma of the colon or rectum with measurable or non-measurable metastatic disease (as per RECIST version 1.1) and an ECOG performance status score of 0 or 1 [16, 17]. Patients had to have received prior treatment with locally available and approved standard therapies and had disease progression during or within 3 months after the last administration of the last standard therapy (or within 6 months of stopping adjuvant oxaliplatin [17]) or discontinuation of standard therapy because of unacceptable toxicity [16, 17]. Patients enrolled in CORRECT were required to have received prior treatment with as many of the following as were licensed in the individual countries: fluoropyrimidine, oxaliplatin, irinotecan and bevacizumab, as well as cetuximab or panitumumab in patients with *KRAS* wild-type tumours [16]. In CONCUR, patients had to have received ≥2 previous treatments, including a fluoropyrimidine plus oxaliplatin or irinotecan; patients

Table 1 Key pharmacological properties of regorafenib

Pharmacodynamic properties
Potent inhibitor of multiple tyrosine kinases, including kinases involved in tumour angiogenesis (VEGFR1, -2, -3, TIE2), oncogenesis (KIT, RET, RAF-1, BRAF, BRAFV600E), metastasis (VEGFR3, PDGFR, FGFR) and tumour immunity (CSF1R) [5, 9]
Does not inhibit kinases of the EGFR family, the protein kinase C family, cyclin-dependent kinases, insulin and IGFR kinase, MET, MEK, ERK1/2 and AKT [9]
Major human metabolites of REG (M-2 and M-5) exhibited similar effects in vitro and in vivo models [10]
Inhibited tumour angiogenesis, tumour cell proliferation, tumour growth and metastasis, and reduced the levels of infiltrating tumour-associated macrophages in xenograft models, including CRC models [9, 11]
Curbed TGF-β1-induced epithelial-to-mesenchymal transition/invasion in vitro by activating PTPase SHP-1-dependent p-STAT3Tyr705 suppression, and inhibited lung metastatic outgrowth of a human CRC cell-line in vivo [12]
Demonstrated antitumour activity in pts with advanced solid tumours [13], including those with advanced CRC [14]
Did not prolong QTc to a clinically relevant extent [15]
Pharmacokinetic properties [5–7]
Mean peak plasma concentration of REG (≈2.5 mg/L) reached ≈3–4 h after single-dose REG 160 mg in pts with advanced solid tumours
Administration with high-fat meal ↑ AUC of REG and ↓ AUC of M-2 and M-3 versus fasted state; therefore, administer with low-fat meal
Systemic exposure to REG at steady-state increased less than dose proportionally at doses >60 mg; accumulation at steady state was ≈twofold
Multiple plasma concentration curves for REG and metabolites are observed over the 24-h dosing interval due to enterohepatic circulation
REG, M-2 and M-5 are highly plasma protein bound (99.5, 99.8 and 99.95%, respectively)
Metabolized primarily in the liver by oxidative metabolism via CYP3A4, and glucuronidation by UGT1A9
Mean plasma elimination half-life of REG and M-2 is 20–30 h and of M-5 is ≈60 h
Renal (any severity) or mild/moderate hepatic impairments do not affect REG, M-2, M-5 exposure; no data for severe hepatic impairment
Avoid coadministration with strong CYP3A4 inducers (AUC: REG ↓ and M-5 ↑), strong CYP3A4 inhibitors (AUC: REG ↑, and M-2 and M-5 ↓) or UGT1A9 inhibitor (coadministration not studied)
Coadministration with a BCRP substrate ↑ AUC of BCRP substrate; monitor for BCRP substrate-related toxicity

AUC area under the plasma concentration time-time curve, *BCRP* Breast Cancer Resistance Protein, *BRAFV600E* BRAF with the V600E mutation, *CRC* colorectal cancer, *CSFIR* colony-stimulating factor 1 receptor, *EGFR* epidermal growth factor receptor, *FGFR* fibroblast growth factor receptor, *IGFR* insulin-like growth factor receptor, *pts* patients, *PTPase* protein tyrosine phosphatase, *PDGFR* platelet-derived growth factor receptor, *RAF* rapidly accelerated fibrosarcoma, *REG* regorafenib, *RET* rearranged during transfection, *SHP-1* SH2-domain-containing phosphatase 1 *TGF* transforming growth factor, *TIE2* tyrosine kinase with immunoglobulin and EGFR homology domain 2, *UGT* Uridine 5'-diphospho-glucuronosyltransferase, *VEGFR* vascular endothelial growth factor receptor, ↑ increase, ↓ decrease

with prior bevacizumab and/or cetuximab/panitumumab therapy (if they have *RAS*-wild-type tumours) were permitted [17]. In both studies, patients had to have a life expectancy of ≥ 3 months and adequate bone marrow, liver and renal function at baseline [16, 17].

Patients were randomized to receive best supportive care plus the approved dosage of regorafenib (160 mg once daily for the first 3 weeks of a 4 week cycle) or placebo until disease progression, death, unacceptable toxicity, withdrawal of consent or decision by the physician to discontinue therapy [16, 17]. The mean duration of treatment with regorafenib and placebo in CORRECT was 2.8 and 1.8 months, respectively, and in CONCUR was 4.0 and 1.6 months.

Baseline characteristics were generally similar between the treatment groups in the individual studies [16, 17], with the exception of numerically fewer patients with *KRAS* mutation in the regorafenib group than in the placebo group of CORRECT [16] (Table 2). Efficacy analyses were based on the intent-to-treat population and the primary endpoint was overall survival (OS) [16, 17]. In CORRECT, a first interim analysis for futility was to be conducted when approximately 30% of the expected 582 deaths had occurred and a second interim analysis for efficacy and futility was to be undertaken when approximately 70% of deaths had occurred [16]. At the time of the preplanned second interim analysis, the study was to be stopped for efficacy if the one-sided p value was ≤ 0.009279, roughly corresponding to a HR of ≤ 0.7864 [16].

In addition to CORRECT and CONCUR, a large, prospective, open-label, phase 3b study of regorafenib, CONSIGN ($n = 2872$ assigned to treatment), assessed safety as the primary objective and progression-free survival (PFS) as the only efficacy outcome [20]. CONSIGN included patients with mCRC who had progressed after approved standard therapies and had an ECOG performance status of 0 or 1; patients received the approved dosage of regorafenib during treatment.

2.1.1 Primary Analyses

The addition of regorafenib to best supportive care relative to the addition of placebo significantly prolonged OS in patients with mCRC who had progressed on previous standard therapy. In CORRECT, the primary endpoint of OS was met at the time of the second interim analysis. OS was significantly prolonged by 1.4 months in regorafenib compared with placebo recipients, corresponding to a 23% reduction in the risk of progression or death ($p = 0.0052$; Table 3) [16]. Similarly, in CONCUR, OS was significantly increased by 2.5 months in patients receiving regorafenib relative to those receiving placebo, corresponding to a 45% reduction in the risk of progression or death ($p = 0.00016$) (Table 3) [17]. Median PFS was significantly longer and the disease control rate was significantly greater with regorafenib relative to placebo in both studies (Table 3) [16, 17]. Although the objective response rate (ORR) in CONCUR was significantly greater in regorafenib than placebo recipients, few patients in either treatment group of the individual studies achieved objective responses (Table 3); all responses were partial and no patient achieved a complete response [16, 17].

Table 2 Key baseline characteristics

Baseline characteristics	CORRECT [16]	CONCUR [17]
	REG/PL	REG/PL
Median age (years)	61/61	58/56
Male (%)	62/60	63/49
Prior therapies ≤ 3 (%)	52/53	59/60
Prior targeted therapy (%)	100/100	59/62
Primary site of disease (%)		
Colon	64/68	58/71
Rectum	30/27	39/28
Both	6/5	3/1
KRAS mutation (%)	54/62	34/26
BRAF mutation (%)	4/2	7/9[a]

PL placebo, *REG* regorafenib

[a]As detected by BEAMing in DNA isolates from baseline plasma [19]

HR-QOL in CORRECT and CONCUR was assessed by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and the EuroQol-5 dimension (EQ-5D) questionnaire (higher scores indicate improvement) [16, 17]. In both studies, health-related quality of life (HR-QOL) and health status scores deteriorated from baseline to a generally similar extent in patients receiving regorafenib or placebo. For instance, in the regorafenib and placebo groups in CORRECT, the mean EORTC QLQ-C30 scores decreased by 13.7 and 12.8 points (baseline mean 62.6 and 64.7), the mean EQ-5D index scores decreased by 0.14 and 0.15 (baseline mean 0.73 and 0.74); and the mean EQ-5D visual analogue scale (VAS) scores decreased by 9.9 and 8.5 points (baseline mean 65.4 and 65.8) [16]. Changes from baseline of ≥ 10, 0.6–0.12 and 7–12 points in the respective scores are considered meaningful [16].

PFS results from the large safety study CONSIGN supported the findings of the two randomized studies, with a median PFS of 2.7 months in 2864 patients who received regorafenib [20].

2.1.2 Subgroup Analyses

Prespecified subgroup analyses of OS and PFS in CORRECT suggested that the treatment benefit with regorafenib was generally consistent across a broad patient

Table 3 Efficacy of oral regorafenib in randomized, double-blind, multinational, phase 3 clinical studies in patients with metastatic colorectal cancer

Study (data cut-off)	Treatment[a] (ITT)	Median OS[b] Months (HR; 95% CI)	Median PFS Months (HR; 95% CI)	ORR % (no.) of pts	DCR[c] % pts
CORRECT [16] (21 July 2011)	REG (505)	6.4 (0.77; 0.64–0.94)**	1.9 (0.49; 0.42–0.58)****	1.0 (5)[d]	41****
	PL (255)	5.0	1.7	0.4 (1)[d]	15
CONCUR [17] (29 November 2013)	REG (136)	8.8 (0.55; 0.40–0.77)***	3.2 (0.31; 0.22–0.44)****	4 (6)[d]*	51****
	PL (68)	6.3	1.7	0	7

DCR disease control rate, *HR* hazard ratio (REG vs. PL), *ITT* intent to treat population, *ORR* objective response rate, *OS* overall survival, *PFS* progression-free survival, *PL* placebo, *pts* patients, *REG* regorafenib

*$p = 0.045$, **$p = 0.0052$, ***$p = 0.00016$, ****$p < 0.0001$ vs. PL (all p values are one-sided)

[a]Pts received REG (160 mg once daily for the first 3 weeks of a 4-week cycle) or placebo, in addition to best supportive care

[b]Primary endpoint

[c]Partial response plus stable disease assessed ≥ 6 weeks after randomization

[d]All responses were partial

population [16]. OS results favoured regorafenib over placebo [hazard ratios (HRs) 0.65–0.95] across most subgroups based on demographic and disease characteristics (e.g. age, previous lines of treatment, *KRAS* mutation status; $n = 24$–760), although 95% CIs crossed 1.0 in some subgroups. When stratified on the basis of the primary site of disease, the effect of regorafenib on OS relative to that of placebo appeared to be greater in patients with colon cancer (HR 0.70; 95% CI 0.56–0.89; $n = 495$) than in those with rectal cancer (HR 0.95; 95% CI 0.63–1.44; $n = 220$). In the rectal cancer subgroup, a greater proportion of patients in the placebo group than those in the regorafenib group received post-study anti-cancer therapies (36% vs. 30%), which may explain the apparent lack of OS benefit with regorafenib. In the subgroup of patients with primary disease in both the colon and rectum, OS appeared to be similar between the regorafenib and placebo groups (HR 1.09; 95% CI 0.44–2.70; $n = 44$), although results may be limited by small patient numbers. Apart from PFS in East European patients (HR 0.58; 95% CI 0.20–1.66; $n = 24$), PFS results in subgroup analyses of CORRECT favoured regorafenib over placebo in all subgroups (95% CIs < 1.0), including in patients with colon, rectal or both colon and rectal cancer (HRs 0.55, 0.45 and 0.35, respectively) [16]. In addition, a post hoc subgroup analysis of CORRECT suggested that OS and PFS results were consistent between Japanese ($n = 100$) and ($n = 660$) non-Japanese patients randomized to regorafenib or placebo [18]

Prespecified subgroup analyses of CONCUR [17] and subgroup analyses of CONSIGN [21–23] generally supported the findings from CORRECT.

In addition, a planned exploratory analysis of CONCUR suggested that patients who had not received prior targeted therapy may derive greater OS benefit with regorafenib versus placebo than patients who had previous targeted therapy (HR 0.31; 95% CI 0.19–0.53 vs. HR 0.78; 95% CI 0.51–1.19) [17]. Other exploratory analyses of CORRECT [24] and CONSIGN [25] suggested that regorafenib recipients who had a PFS of > 4 months (19% and 23% of patients in the respective studies) may have better performance status scores [24, 25], fewer metastatic tumour sites [24], no liver involvement [25] and longer time since diagnosis of metastatic disease [24, 25] than patients with PFS ≤ 4 months (81% and 77% of patients).

2.1.3 Potential Predictive or Prognostic Markers

Several retrospective analyses of the phase 3 studies evaluated potential markers/parameters to predict outcomes with regorafenib. The RadioCORRECT study, based on data from 202 patients in CORRECT, showed that RECIST 1.1 and the change in the sum of target lesion diameters (from baseline to week 8), as assessed by contrast-enhanced computed tomography, predict favourable outcomes with regorafenib [26]. Results showed that the disease control rate was higher (53.4% vs. 20.6%) and the median change in lesion diameter (4% vs. 21%) was smaller with regorafenib than placebo (both $p < 0.001$), supporting early radiological assessment of tumour response for clinical decision making, and continuation of treatment in patients who have stable disease [26].

Another retrospective exploratory analysis of CORRECT showed a consistent benefit of regorafenib over placebo in terms of OS and PFS across a range of patient subgroups based on *KRAS* and *PIK3CA* mutation status (assessed by BEAMing technology) [27]. Treatment benefit was also seen regardless of circulating total human genomic DNA levels or plasma levels of protein biomarkers of angiogenesis [e.g. angiopoietin-2, interleukin (IL)-8, placental growth factor (P1GF)] and/or pathogenesis of

CRC (e.g. bone morphogenetic protein 7, macrophage colony-stimulating factor), according to multivariate analyses of CORRECT [27] and CONCUR [28]. There was also no association between clinical efficacy of regorafenib and single-nucleotide polymorphisms in the VEGF-A signalling pathway [29] or microsatellite instability [30] in the CORRECT study. Density reduction of liver metastases was also assessed as a potential predictive parameter of benefit with regorafenib, but results were variable between RadioCORRECT [26] and a small analysis in 42 patients from CORRECT and CONSIGN [31].

In terms of prognostic markers of mCRC, an analysis of plasma samples from patients in CORRECT suggested that baseline circulating DNA levels and plasma levels of IL-8 and P1GF may be prognostic for clinical outcomes with regorafenib, with high levels of these associated with shorter median OS in multivariate analyses (p value not available) [27]. It has been hypothesized that the level of metastatic burden may be represented by the amount of tumour-derived DNA in the circulation; however, the process for the release of DNA from metastatic lesions is unclear [27]. In addition, the protein biomarker analysis of CONCUR showed that elevated levels of angiopoietin-2 and VEGF-A were associated with poor OS, and elevated levels of angiopoietin-2, VEGF-A, insulin-like growth factor binding protein 2, von Willebrandt Factor and IL-8 were associated with poor PFS (all $p < 0.05$) [28].

2.2 Real-World Studies

Several large ($n > 400$) real-world studies, REBECCA [32], CORRELATE [33], a Japanese postmarketing study [34] and RECORA [35], supported the efficacy of regorafenib in patients with mCRC. The median OS (5.6–7.0 months) in patients receiving regorafenib in these studies (Table 4) was consistent with that in the phase 3 studies (Table 3). In addition to the efficacy and safety of regorafenib, the REBECCA study assessed prognostic factors associated with treatment outcomes and found that OS was independently and unfavourably associated with poor performance status (> 0), short time from initial diagnosis of metastases to the start of regorafenib treatment (< 18 months), low initial regorafenib dose (< 160 mg), > 3 metastatic sites, presence of liver metastases and presence of *KRAS* mutations (all $p < 0.05$) [32]. On combining these factors, three prognostic groups of patients were identified who derived minimum, moderate or maximum benefits with regorafenib. These groups were patients with low (34% of patients), intermediate (42% of patients) and high (24% of patients) risk of death who had a median OS of 9.2, 5.2 and 2.5 months, respectively [32]. The RECORA study also showed significant between-group differences in OS when regorafenib recipients were stratified according to ECOG performance status (0 or 1 vs. 2) and time from initial diagnosis (< 18 vs. ≥ 18 months) (no quantitative data available) [35]. Additional studies are needed to confirm these findings and to assess whether these variables are of prognostic and/or predictive value in patients receiving regorafenib [32].

3 Tolerability of Regorafenib

Regorafenib has a manageable tolerability profile based on data from > 4800 patients (4518 patients received regorafenib monotherapy) enrolled in clinical studies, including phase 3 studies in 636 patients with mCRC, 132 patients with gastrointestinal stromal tumours, 374 patients with hepatocellular carcinoma and 2864 patients in the CONSIGN expanded access study [5, 6]. The most common (incidence ≥ 30%) adverse reactions with regorafenib

Table 4 Efficacy of regorafenib in patients with metastatic colorectal cancer during routine clinical use

Study	Region	No. of pts	% pts with initial REG dose 160 or ≤ 120 mg	Treatment duration (months)	OS (median)	Other efficacy outcomes
REBECCA [32] (cohort)	France	654 (FAS)	80/20	2.2 (median)	5.6	12-month OS: 22%
CORRELATE[a] [33] (observational)	Europe, Latin America, Asia	500 (IA)	53/46	2.4 (median)	6.5	12-month OS: 27%
Japanese PMS[a] [34]	Japan	787 (IA)	66/22	NR	7.0	TTF: 2.1 months (median)
RECORA[a] [35] (observational)	Germany	463	NR	2.7 (mean)	5.8	PFS: 3.1 months (median) TTP: 4.0 months (median)

REBECCA is a cohort study nested within a compassionate use program

FAS full analysis set, *IA* interim analysis, *NR* not reported, *OS* overall survival, *PFS* progression-free survival, *PMS* postmarketing study, *REG* regorafenib administered once daily for the first 3 weeks of a 4 week cycle *TTF* time to treatment failure, *TTP* time to progression

[a]Abstract presentations

were pain, hand-foot skin reaction (HFSR), asthenia/fatigue, diarrhoea, decreased appetite and food intake, hypertension and infection; the most common serious adverse reactions with regorafenib were severe liver injury, haemorrhage, gastrointestinal (GI) perforation and infection [5].

Abnormalities of liver function tests, including elevations of ALT, AST and bilirubin levels, were reported very frequently (incidence ≥ 1/10) in regorafenib recipients in clinical trials across all indications [5, 6]. Liver dysfunction in patients receiving regorafenib usually occurred within the first 2 months of therapy and was characterized by a hepatocellular pattern of injury with transaminase elevations of > 20 times the upper limit of normal [5, 6] Severe drug-induced liver injury with fatal outcome occurred at a higher incidence in Japanese than non-Japanese patients (≈ 1.5% vs. < 0.1%) [5].

GI perforation (including fatal events) and fistulae have been reported in < 1% of patients receiving regorafenib monotherapy in clinical trials across all indications [6]. These events are known to occur commonly as disease-related complications in patients with intra-abdominal malignancies [5].

Adverse skin reactions, including HFSR and severe rash requiring dose modifications, were also very common with regorafenib in placebo-controlled studies across all indications (incidence 71.9% vs. 25.5% with placebo) [6]. HFSR, mostly of mild or moderate severity, occurred in 53% of regorafenib recipients compared with 8% of placebo recipients, with a higher incidence seen in Asian patients receiving regorafenib (72%). Grade 3 HFSR was reported in 16% of regorafenib recipients (18% of Japanese patients) and < 1% of placebo recipients. Most cases of HFSR occurred during the first cycle of treatment [5, 6].

Hypertension and haemorrhage, usually of mild or moderate severity, were very common (incidence ≥ 1/10) in patients receiving regorafenib in clinical studies across all indications [5, 6]. In placebo-controlled studies, few regorafenib recipients (≤ 3.0%) had hypertensive crisis, grade ≥ 3 haemorrhage or fatal haemorrhagic events (including cerebral, respiratory, GI and genitourinary events). In most patients, the onset of hypertension occurred during the first cycle of treatment.

Regorafenib has also been associated with an increased risk of infections, with most cases being of mild or moderate severity. Any-grade infections occurred in 32% of regorafenib compared with 17% of placebo recipients across all placebo-controlled studies, with the most common events being urinary tract infections (5.7%), nasopharyngitis (4.0%), mucocutaneous and systemic fungal infections (3.3%) and pneumonia (2.6%). Infections with fatal outcomes were rare, occurring in 1% of regorafenib and 0.3% of placebo recipients, with the most common fatal infections being respiratory (0.6 vs. 0.2% of patients) [5, 6].

The US, EU and Japanese prescribing information carry several warnings and precautions related to adverse reactions with regorafenib, with baseline assessment, periodic monitoring, dose reduction, treatment interruption and/or discontinuation of therapy recommended for their management [5–7]. Local prescribing information should be consulted for further details.

3.1 In Patients with Metastatic Colorectal Cancer

The tolerability profile of regorafenib in the phase 3 studies and real-world studies (Sect. 2) in patients with mCRC was consistent with that in the other indications. In the CORRECT study, which involved largely white patients, 93% of patients receiving regorafenib in addition to best supportive care had treatment-related adverse events (AEs) during treatment and 30 days after discontinuation of therapy, compared with 61% of patients receiving placebo in addition to best supportive care [16]. Most AEs occurred early during the course of treatment (in cycles 1 and 2), were of mild or moderate severity (Fig. 1) and manageable with dose reductions or interruptions. The most common treatment-related any-grade AEs with regorafenib included fatigue and HFSR (Fig. 1). Treatment-related grade 3 or 4 AEs occurred in 54% of patients receiving regorafenib compared with 14% of patients receiving placebo, with HFSR, fatigue, diarrhoea and hypertension occurring most commonly (Fig. 1) [16].

Laboratory abnormalities were more frequent in patients receiving regorafenib than in those receiving placebo, including treatment-related any-grade thrombocytopenia (13% vs. 2%), hyperbilirubinemia (9% vs. 2%) proteinuria (7% vs. 2%), anaemia (7% vs. 2%) and hypophosphatemia (5% vs. < 1%) [16]. The most common treatment-related grade 3 or 4 laboratory abnormalities with regorafenib were hypophosphatemia (4% vs. 0.4%) and thrombocytopenia (3% vs. 2%). Treatment-emergent liver function abnormalities occurred at numerically higher incidences in the regorafenib group than the placebo group, including increased levels of ALT (45% vs. 30%), AST (65% vs. 46%) and bilirubin (45% vs. 17%), with the between-group difference largely because of grade 1 or 2 events. Grade 3 elevations in transaminases occurred in ≈ 5% of regorafenib and 3–4% of placebo recipients and grade 4 elevations in 0.6 and 0.6% of patients, respectively; grade 3 increases in bilirubin were reported in 10 and 5% of patients and grade 4 increases in ≈ 3% of patients in both groups [16].

Serious AEs (SAEs) occurred in 44% of regorafenib and 40% of placebo recipients [16], with numerically higher incidences of pyrexia (2.8% vs. 0.4%), abdominal pain (2.4% vs. 0.8%), diarrhoea (1.6% vs. 0%), hepatic failure (1.4% vs. 0.8%), haemorrhages (1.0% vs. 0%) and jaundice (0.4% vs. 0%) in regorafenib than placebo recipients [10].

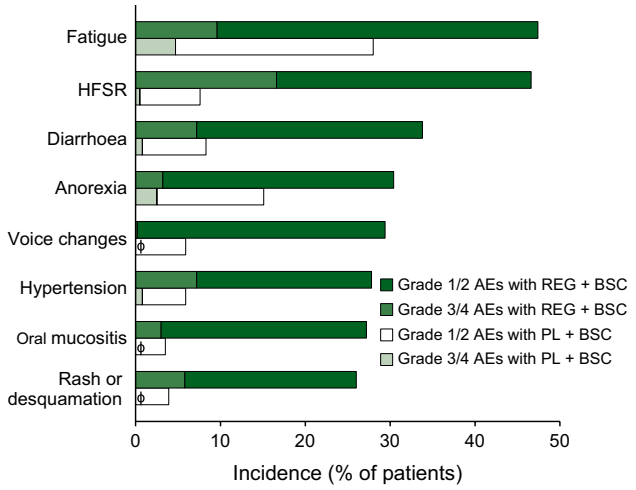

Fig. 1 Any-grade treatment-related adverse events (according to NCI Common Terminology Criteria for Adverse Events version 3.0) occurring in > 20% of patients receiving either regorafenib plus best supportive care or placebo plus best supportive care in the CORRECT study [16]. *AEs* adverse events, *BSC* best supportive care, *HFSR* hand-foot skin reaction, *REG* regorafenib, *PL* placebo, *ϕ* indicates incidence 0%

Sixty-nine patients in the regorafenib group and 41 patients in the placebo group died, largely because of progression of underlying disease (58 and 35 deaths, respectively) [16]. Eight deaths in the regorafenib group and three deaths in the placebo group were attributed to AEs not related to disease progression. AEs associated with fatalities in regorafenib recipients were pneumonia and GI bleeding (two patients each), and intestinal obstruction, pulmonary haemorrhage, seizure and sudden death (one patient each); AEs associated with fatalities in placebo recipients were pneumonia (two patients) and sudden death (one patient). The incidence of thromboembolism did not differ between the regorafenib and placebo groups (2% in both groups) [16].

Dose modifications because of AEs were required in almost three times as many regorafenib as placebo recipients (67% vs. 23%), with 38% of patients in the regorafenib group and 3% of patients in the placebo group requiring dose reductions, and 61% and 22% of patients requiring dose interruptions [16]. The most common AEs that led to dose modifications were dermatological, GI, constitutional, and metabolic or laboratory events. Treatment was discontinued because of AEs in 17.6% of regorafenib compared with 12.6% of placebo recipients [10].

Results from the large, open-label CONSIGN study were consistent with the results in CORRECT [20]. Following median treatment of 2.5 months, 99% of patients had treatment-emergent AEs and 80% had treatment-related AEs, which led to treatment discontinuation in 25% and 9% of patients, respectively. Treatment-related SAEs were reported in 44% of patients, leading to treatment discontinuation in 9% of patients. The most common (incidence > 10%) AEs of grade ≥ 3 severity were fatigue (18%), hypertension (17%), and HFSR (14%); treatment-emergent laboratory abnormalities of grade ≥ 3 severity included elevated levels of bilirubin (13%), AST (7%) and ALT (6%). There was one non-fatal case of severe drug-induced liver injury during extended monitoring [20].

3.1.1 In Asian Patients

The nature of AEs with regorafenib in the CONCUR study ($n = 204$) in Asian patients (> 90% East Asian patients) was generally similar to that in the CORRECT study [17]. However, the incidence of treatment-related any-grade HFSR with regorafenib in CONCUR appeared to be higher than in the overall population of CORRECT (74% and 47% of patients, respectively) [17]. The incidence of grade 3 treatment-related HFSR in patients receiving regorafenib in CONCUR was similar to that in overall population of CORRECT (16% and 17%) [16, 17]. Treatment-emergent liver enzyme increases of any-grade severity also occurred at numerically higher incidences in CONCUR [5] than in the overall population of CORRECT [16], with ALT elevations occurring in 54% and 45% of patients in the respective studies, AST elevations in 70% and 65% of patients, and bilirubin elevations in 67% and 45% of patients [5, 16]. AE-related discontinuation rates in CONCUR were 14% and 6% in regorafenib and placebo groups, respectively [17].

The tolerability profile of regorafenib in Japanese patients ($n = 100$) in the CORRECT study was generally similar to that in the other Asian patients. Japanese patients had higher incidences (≥ 20% greater) of treatment-related any-grade HFSR (80% vs. 42%), hypertension (60% vs. 23%), proteinuria (40% vs. 2%), thrombocytopenia (39% vs. 9%) and increased lipase levels (25% vs. 2%) than non-Japanese patients in CORRECT, while the incidence of diarrhoea appeared to be lower in Japanese patients (22% vs. 36%) [18]. Treatment-related any-grade liver enzyme elevations with regorafenib were also more frequent in Japanese patients than in non-Japanese patients, with ALT elevations reported in 12% and 1% of patients, AST elevations in 19% and 2% of patients and bilirubin elevations in 15% and 8% of patients. Grade 3 or 4 treatment-related liver enzyme elevations with regorafenib occurred in 2–6% of Japanese patients and ≤ 2% of non-Japanese patients. Most AEs were manageable with dosage modifications, with 84.6% of Japanese and 51.3% of non-Japanese patients requiring dose adjustments, and 13.8% and 7.4% of patients, respectively, discontinuing treatment because of treatment-related AEs [18]. There was one fatal case of regorafenib-related, drug-induced liver injury, which was reported 43 days after the first dose of regorafenib in a 62-year-old man who had liver metastases

and progressive liver dysfunction, which led to his death 6 weeks later [16, 18].

4 Dosage and Administration of Regorafenib

In the EU, regorafenib monotherapy is indicated for the treatment of adults with mCRC who have been previously treated with, or are not considered candidates for available therapies, including fluoropyrimidine-based chemotherapy, an anti-VEGF therapy and an anti-EGFR therapy [5]. In the USA, 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 *RAS* wild-type, an anti-EGFR therapy [6]. Regorafenib is also approved in Japan for the treatment of unresectable, advanced/recurrent CRC [7]. The recommended dosage of regorafenib is 160 mg taken orally once daily for the first 21 days of each 28-day cycle [5–7], with treatment until unacceptable toxicity (US and EU), or disease progression (US) or as long as benefit is observed (EU) [5, 6]. Regorafenib should be taken at the same time each day with a light (low-fat) meal [5, 6]. Dosage adjustments, interruptions or discontinuation of therapy may be required for the management of AEs associated with regorafenib [5–7]; the US and Japanese prescribing information carry boxed warnings regarding hepatoxicity with regorafenib therapy [6, 7]. Where reported, no dosage adjustment of regorafenib is required in patients with mild, moderate or severe renal impairment (US and EU), or in patients with mild (US and EU) or moderate (US) hepatic impairment; regorafenib is not recommended for patients with severe hepatic impairment (Table 1) [5, 6].

5 Place of Regorafenib in the Management of Metastatic Colorectal Cancer

Current treatment guidelines include regorafenib and trifluridine/tipiracil as third- [2, 36] or subsequent- [3, 4] line treatment options for the control of progression or cytoreduction in patients with mCRC [2–4, 36], with the ESMO [2] and Pan-Asian [36] guidelines recommending these agents as the preferred choices for patients with *RAS* or *BRAF* mutations.

Regorafenib is a multiple kinase inhibitor (Table 1) with demonstrated efficacy in patients with mCRC who have progressed after failure of standard therapy and have a very poor prognosis (Sect. 2). Two well-designed phase 3 studies, CORRECT and CONCUR, showed that the addition of regorafenib monotherapy to best supportive care relative to the addition of placebo significantly prolonged OS (primary endpoint) by up to 2.5 months and PFS by up to 1.5 months, with the main effect of the drug being disease stabilization rather than tumour shrinkage (Sect. 2.1.1). HR-QOL was not adversely affected with regorafenib monotherapy compared with placebo (Sect. 2.1.1). Results from the open-label phase 3 CONSIGN study and large real-world studies supported the efficacy of regorafenib (Sect. 2).

Prespecified subgroup analyses of OS and PFS in the phase 3 studies suggested that the treatment benefit with regorafenib was generally consistent across a broad patient population, regardless of demographic and disease characteristics (Sect. 2.1.2). Although cross-trial comparisons are not appropriate due to potential differences between studies (e.g. study populations and treatment strategies), the OS benefit with regorafenib appeared to be greater in CONCUR than in CORRECT (Table 3), which, according to the CONCUR study authors, could be because of the difference in the proportion of patients with prior targeted therapy [17] (100% and ≈ 60%, in the respective studies; Table 2). A planned exploratory analysis of CONCUR also suggested that patients who had not received prior targeted therapy may have greater OS with regorafenib than patients who had received prior treatment with these agents (Sect. 2.1.2). However, these results should be interpreted with caution as they were exploratory and confounded by small patient numbers, as well as imbalances between regorafenib and placebo groups in terms of post-study treatments in some of the subgroups based on prior targeted therapy [17]. Other exploratory analyses of CORRECT and CONSIGN suggested that some patient characteristics (e.g. better performance status scores, fewer metastatic tumour sites and longer time since diagnosis of metastatic disease) may be associated with longer PFS (> 4 months) (Sect. 2.1.2). However, further robust data are needed to confirm these observations.

The tolerability profile of regorafenib in patients with mCRC was consistent with that of a typical small-molecule multiple kinase inhibitor, with the most frequent AEs with regorafenib being fatigue and HFSR (Sect. 3.1). The majority (> 90%) of patients receiving regorafenib experienced AEs, although most were of mild or moderate severity, occurred early during treatment and were generally manageable with dose reductions or treatment interruptions (Sect. 3). Laboratory abnormalities, including liver enzyme elevations, were very common with regorafenib, most of which were of mild or moderate severity. However, there have been rare instances of severe drug-induced liver injury with fatal outcomes in patients receiving regorafenib in clinical trials across all indications (Sect. 3). There are boxed warnings regarding hepatoxicity with regorafenib in the US and Japanese prescribing information; monitoring of hepatic function prior to and during treatment is recommended, and dosage reduction, treatment interruption or discontinuation of therapy may be required [5, 6]. Asian patients appeared to be at higher risk of HFSR and liver enzyme elevations than non-Asian patients (Sect. 3).

In addition to the therapeutic efficacy and tolerability, the cost effectiveness of treatment is an important consideration. A pharmacoeconomic analysis conducted from the US payer perspective, based on data from the CORRECT study in patients with mCRC and drug costs based on Medicare reimbursement rates in 2014, estimated that regorafenib would provide minimal incremental benefit at high incremental cost per quality of life-year (QALY) gained when used as third-line treatment of mCRC relative to best supportive care [37]. The estimated incremental cost-effectiveness ratios of regorafenib relative to best supportive care ranged between US$730,000 to 980,000/QALY gained [37]. Additional, well-designed pharmacoeconomic analyses based on current pricing and payment methods are warranted.

There has been some discussion in the literature regarding the high absolute prices of more recently developed oncology drugs and the cost per month of value gained with treatment [38]. According to one analysis, some oncology drugs, such as panitumumab and regorafenib in patients with mCRC, appear to be associated with lower monthly costs than some pre-existing dugs (e.g. the monthly cost of regorafenib in 2014 was estimated as $US9919 versus $US11,862 for cetuximab) [38]. Moreover, using data from two exploratory analyses conducted from the Spanish [39] and French [40] perspectives, it was estimated that third-line targeted therapies (regorafenib and cetuximab) have lower incremental costs per month of median OS gained than first-line therapies, which in turn were associated with lower costs than second-line therapies [38]. These results suggest that more recently developed oncology drugs for mCRC may provide additional value at lower costs than pre-existing treatments; however, further studies are needed to confirm these observations.

Owing to the modest OS and marginal PFS benefit with regorafenib, several retrospective analyses of the phase 3 studies were undertaken to identify potential markers/parameters for predicting outcomes with regorafenib and improving the cost-benefit ratio (Sect. 2.1.3). For instance, the Radio-CORRECT study suggested that assessment of treatment response by RECIST and evaluation of tumour response at week 8 as a continuous variable predict favourable outcomes with regorafenib (Sect. 2.1.3). Several other studies have also assessed potential predictive or prognostic biomarkers of clinical benefit with regorafenib, including baseline serum CCL5 level (which was associated with tumour shrinkage, and better PFS and OS) [41]; decrease in serum VEGF-A [41] or Carbohydrate Antigen 19-9 [42] levels (associated with better PFS); high platelet count and high neutrophil/lymphocyte ratio (associated with worse OS) [43]; high lymphocyte count (associated with better OS) [43]; early morphological change (associated with better PFS and OS) [44]; and genetic polymorphisms in the *CCL5/CCR5* pathway (some variants associated with better OS and/or PFS) [45]. However, the clinical usefulness, if any, of these and other markers/factors for predicting outcomes with regorafenib remains to be confirmed.

AEs such as cutaneous toxicity (e.g. HFSR), hypertension and GI AEs are drug-class effects associated with the mechanism of action of targeted therapies such as VEGF inhibitors [46]. An association between these mechanism-based AEs and clinical outcomes with targeted therapy has also been suggested. For example, in patients with mCRC treated with bevacizumab, a significant ($p < 0.05$) association between improvements in OS, PFS and ORR and the occurrence of hypertension was observed [47]. With regorafenib, a retrospective exploratory analysis of CORRECT suggested that patients who had HFSR had greater OS (9.5 vs. 4.7 months; HR 0.41; 95% CI 0.32–0.53) and PFS (3.4 vs. 1.8 months; 0.54; 95% CI 0.45–0.66) than patients who did not have HFSR [48]. Another study in 102 patients with mCRC treated with the approved dose of regorafenib found that OS was significantly ($p < 0.05$) associated with HFSR and rash, and time to treatment failure was significantly associated with HFSR, neutropenia and AST elevations of grade > 2, suggesting that these AEs may be surrogate markers of efficacy [49]. Additional well-designed studies are needed to confirm these observations and establish predictive markers of regorafenib efficacy.

Toxicities associated with regorafenib limit its use in clinical practice. To optimise therapy, a phase 2, randomized study (ReDOS) compared weekly regorafenib dose escalation (from 80 mg to 160 mg once daily, as tolerated) with standard dose regorafenib 160 mg once daily [50]. Recently presented results showed significant benefits with the dose-escalation strategy relative to standard therapy in terms of the proportion of patients completing 2 cycles of therapy and initiating cycle 3 ($p = 0.028$), a well as HR-QOL and tolerability benefits [50]. Based on these results, the regorafenib dose-escalation protocol has been included as a dosing strategy in the NCCN colon and rectal cancer guidelines [3, 4].

There are no direct head-to-head comparisons of regorafenib and trifluridine/tipiracil, which is also approved for use as third- or subsequent-line therapy in patients with refractory mCRC. Results from a retrospective analysis [51] and a propensity score observational study (REGOTAS) [52] in Japanese patients with refractory mCRC suggested that regorafenib and trifluridine/tipiracil have generally similar efficacy, but different tolerability profiles, which could impact the choice of therapy for individual patients. While regorafenib was associated with higher incidences of non-haematological toxicities (e.g. HFSR, liver dysfunction, hypertension), trifluridine/tipiracil had higher incidences of haematological toxicities (e.g. neutropenia, anaemia, thrombocytopenia) [51, 52].

These differences should be taken into consideration when determining treatment for individual patients, particularly in patients such as those who have disease progression after cytotoxic therapy and who have poor bone marrow function, or those who have severe HFSR with prior capecitabine therapy [53]. There are no data regarding the order of administration of these agents if sequential administration is being considered [53].

To conclude, regorafenib is associated with a modest, but significant improvement in OS and has a generally manageable tolerability profile in patients with mCRC who have progressed on standard therapy. Although identification of biomarkers/parameters predicting efficacy outcomes with regorafenib will help to individualize therapy, current evidence indicates that regorafenib is a valuable treatment option for patients with refractory mCRC who have a very poor prognosis.

Data Selection Regorafenib: 585 records identified	
Duplicates removed	113
Excluded during initial screening (e.g. press releases; news reports; not relevant drug/indication; preclinical study; reviews; case reports; not randomized trial)	334
Excluded during writing (e.g. reviews; duplicate data; small patient number; nonrandomized/phase I/II trials)	84
Cited efficacy/tolerability articles	23
Cited articles not efficacy/tolerability	31
Search Strategy: EMBASE, MEDLINE and PubMed from 2014 to present. Previous Adis Drug Evaluation published in 2014 was hand-searched for relevant data. Clinical trial registries/databases and websites were also searched for relevant data. Key words were regorafenib, Stivarga, BAY734506, metastatic colorectal cancer. Records were limited to those in English language. Searches last updated 8 June 2018.	

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Compliance with Ethical Standards

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