Drugs (2015) 75:1009–1017
DOI 10.1007/s40265-015-0406-x



# Regorafenib: A Review of Its Use in Patients with Advanced Gastrointestinal Stromal Tumours

**Matt Shirley**[1] · **Gillian M. Keating**[1]

Published online: 22 May 2015


**Abstract** Regorafenib (Stivarga®) is an orally administered small molecule inhibitor of multiple protein kinases, including kinases involved in oncogenesis and tumour angiogenesis. It was initially approved for use in patients with previously treated metastatic colorectal cancer. Based on the findings of the phase III GRID clinical trial, approval for regorafenib has been expanded to include the treatment of advanced gastrointestinal stromal tumours (GISTs) following the failure of imatinib and sunitinib. In the GRID trial, regorafenib significantly improved progression-free survival and was associated with a significantly higher disease control rate than placebo. No significant between-group difference was observed in overall survival (OS) in the trial; however, the high proportion of patients who crossed over from placebo to regorafenib likely impacted the OS analysis. Regorafenib has an acceptable tolerability profile, with most adverse events being manageable with dose modification and/or supportive measures. The most commonly reported drug-related adverse events among patients receiving regorafenib in the GRID trial were hand-foot skin reaction, hypertension, diarrhoea and fatigue. In conclusion, regorafenib presents a valuable new tool in the treatment of patients with advanced GISTs following the failure of imatinib and sunitinib.

| Regorafenib in advanced gastrointestinal stromal tumours: a summary |
|---|
| An orally administered multikinase inhibitor with activity against kinases involved in oncogenesis and tumour angiogenesis |
| Significantly prolongs progression-free survival and improves the disease control rate after failure of imatinib and sunitinib |
| A significant improvement in overall survival is yet to be demonstrated, although trial data were impacted by a high rate of cross-over |
| An acceptable tolerability profile, with adverse events generally being manageable with dose modification and/or supportive measures |
| The most common drug-related adverse events are hand–foot skin reaction, hypertension, diarrhoea and fatigue |

## 1 Introduction

Although rare, gastrointestinal stromal tumours (GISTs) represent the most common mesenchymal tumours of the gastrointestinal (GI) tract [1, 2]. Surgery remains the standard treatment for localized GISTs [3, 4]. Cytotoxic chemotherapy has not generally been effective and, until the development of targeted therapies, the prognosis for

**The manuscript was reviewed by**: ***C. R. Garrett***, Department of Gastrointestinal Medical Oncology, University of Texas MD Anderson Cancer Center, Houston, TX, USA; ***P. Rutkowski***, Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland.

✉ Matt Shirley
demail@springer.com

[1] Adis, Level 1, 5 The Warehouse Way, Northcote 0627, Private Bag 65901, Mairangi Bay, 0754 Auckland, New Zealand

individuals with locally advanced, unresectable and/or metastatic GISTs was very poor [1, 5]. GISTs commonly carry activating mutations in proto-oncogenes encoding tyrosine kinases [e.g. KIT, platelet-derived growth factor receptor alpha (PDGFR-α)], leading to enhanced cell proliferation and survival [2, 6, 7]. Subsequent to the molecular studies which identified the role of tyrosine kinases in the pathogenesis of the disease, the tyrosine kinase inhibitor imatinib was developed as a treatment for advanced GISTs [8]. Imatinib, which inhibits KIT, PDGFR-α and the Abl tyrosine kinases, has had a significant impact on the management of GISTs [5, 8] and it remains the first-line therapy for advanced disease [3, 4]. However, around 10–15 % of GISTs exhibit primary resistance to imatinib, and the vast majority of the remaining GISTs will develop secondary resistance to the drug, typically within 2–3 years [2, 5, 6]. Secondary resistance usually occurs through clonal evolution, with selection and expansion of tumour clones harbouring secondary KIT or PDGFR-α mutations [5, 6].

Following imatinib failure, the second-line therapy for advanced GISTs is sunitinib, another tyrosine kinase inhibitor [3, 4, 9]. Besides KIT and PDGFR-α, sunitinib also inhibits several other kinases, including vascular endothelial growth factor receptor (VEGFR) kinases. Sunitinib prolongs progression-free survival (PFS), the time to tumour progression, and overall survival (OS) in GIST patients following imatinib failure [9, 10]. However, as with imatinib treatment, GISTs commonly acquire resistance to sunitinib [11]. Until the approval of regorafenib (Stivarga®), third-line treatment options for patients with advanced GISTs were very limited.

Regorafenib is an orally administered multikinase inhibitor that was initially approved in the treatment of metastatic colorectal cancer (CRC) [12, 13]. Based on the findings of the phase III GRID trial [14], approval for regorafenib has been expanded to include the treatment of advanced GISTs after the failure of imatinib and sunitinib. This article reviews the efficacy and tolerability of oral regorafenib in the treatment of patients with unresectable and/or metastatic GISTs following the failure of imatinib and sunitinib. A discussion of the pharmacological properties of the drug is also included.

## 2 Pharmacodynamic Properties

Regorafenib is a small molecule inhibitor of multiple protein kinases, including kinases involved in normal cellular functions as well as in pathological processes such as oncogenesis (e.g. KIT/mutant $KIT^{K642E}$), tumour angiogenesis (e.g. VEGFR-1, -2, -3 and TIE2), and maintenance of the tumour microenvironment [e.g. PDGFR-α, PDGFR-β, fibroblast growth factor receptor (FGFR)-1 and FGFR-2] [12, 13, 15]. In preclinical studies, regorafenib has exhibited antiproliferative, antiangiogenic, antitumour and antimetastatic effects [15–18].

Besides the kinases mentioned above, in vitro biochemical and cellular phosphorylation assays demonstrated that regorafenib inhibits the following protein kinases at clinically achievable, nanomolar concentrations: RET, the mutant $RET^{C634W}$, RAF-1, BRAF, the mutant $BRAF^{V600E}$, DDR2, Eph2A, PTK5, p38α and p38β [12, 15]. No inhibition of kinases of the protein kinase C or epidermal growth factor receptor families, cyclin-dependent kinases, insulin and insulin growth factor receptor kinase, MET, MEK, ERK1/2 and AKT was observed with regorafenib concentrations of up to 1 μmol/L [15].

Antiproliferative effects of regorafenib were demonstrated in vascular cells and various tumour cell lines [15, 16]. Notably, antiproliferative effects of regorafenib were observed with the GIST882 cell line expressing the mutant receptor $KIT^{K642E}$ [15].

Inhibition of extravasation by regorafenib was demonstrated in rat glioblastoma [15] and mouse orthotopic CRC xenograft models [18] using dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI). Regorafenib also exhibited antiangiogenic effects in GIST [17], colorectal [15, 16, 18] and breast cancer [15] xenograft models in mice. In the GIST model (UZLX-GIST9, harbouring *KIT* exon 11 and exon 17 mutations), regorafenib led to a 1.4-fold reduction in microvessel density ($p < 0.05$ vs. control) [17]. Consistent with the preclinical data, DCE-MRI analyses in phase I studies in patients with advanced solid tumours [19] or CRC [20] also indicated reduced tumour perfusion after regorafenib treatment.

Dose-dependent antitumour activity was exhibited by regorafenib, with the drug inhibiting (or retarding) tumour growth in multiple murine xenograft models, including colorectal, breast and renal cell carcinoma models [15]. Regorafenib 30 mg/kg/day completely suppressed tumour growth ($p < 0.01$ vs. vehicle control) in the mouse orthotopic CRC xenograft model [18], while it was associated with a 30 % reduction in tumour size ($p < 0.05$) in the GIST xenograft model UZLX-GIST9 [17].

Finally, regorafenib prevented the formation of new metastases [16, 18] plus inhibited the growth of established metastases [16] in murine CRC metastasis models.

## 3 Pharmacokinetic Properties

The pharmacokinetic data in this section is primarily drawn from clinical trials in patients with advanced solid tumours, metastatic CRC or advanced GISTs [12, 13, 19–22]. Regorafenib exposure was generally similar across the

different patient groups; however, overall, a large inter-patient variability in exposure to regorafenib was observed [20, 23].

Following regorafenib administration, two major regorafenib metabolites are found in human plasma: M-2 (*N*-oxide metabolite) and M-5 (*N*-oxide/*N*-desmethyl metabolite) [12, 13]. Both M-2 and M-5 display pharmacological activity in vitro, with activity similar to that of the parent compound [12, 13], and thus are predicted to contribute to the therapeutic efficacy of the drug (Sect. 4) [20]. In plasma concentration-time profiles for regorafenib, M-2 and M-5, multiple peaks are observed over the 24-h dosing interval indicating that the compounds undergo enterohepatic circulation (Sect. 3.2) [12, 13, 19].

### 3.1 Absorption and Distribution

Following administration of a single oral 160 mg dose, regorafenib reaches a maximum plasma concentration ($C_{max}$) of 2.5 μg/mL at a median time of approximately 4 h [12, 13]. Compared with a single dose, regorafenib concentrations at steady state are approximately twofold higher, consistent with the long elimination half-life ($t_{½}$) of the drug (Sect. 3.2) and the dosing interval (Sect. 6) [13]. The steady-state plasma concentrations for M-2 and M-5 are comparable to that of the parent compound [12, 13, 19, 20]. Peak-trough fluctuations for regorafenib and its major metabolites are small, with an approximate 1.5- to 3-fold difference between maximum and minimum mean plasma concentrations at steady state [19, 20]. At doses greater than 60 mg, systemic exposure of regorafenib at steady-state increases less than dose proportionally [12, 13, 19]. M-2 and M-5 exhibit non-linear accumulation, possibly because of enterohepatic recycling or saturation of the UDP-glucuronosyltransferase (UGT)-1A9 pathway [13].

In a food effect study, the combined concentrations of regorafenib and the two major metabolites were highest when regorafenib was administered after a low-fat meal (8.2 g of fat) compared to when it was administered after a high-fat meal (54.6 g of fat) or under fasting conditions [12, 13]; therefore, regorafenib should be taken with a low-fat meal (Sect. 6).

Regorafenib and its major metabolites are highly (≥99.5 %) bound to human plasma proteins [12, 13]. The mean apparent volume of distribution of regorafenib at steady state is 88 L [23].

### 3.2 Metabolism and Elimination

Metabolism of regorafenib primarily occurs in the liver through oxidative metabolism mediated by cytochrome P450 (CYP) 3A4 and glucuronidation mediated by UGT1A9 [12, 13]. Besides M-2 and M-5, six minor metabolites have been identified in plasma [13]. Metabolites may also undergo reduction or hydrolysis in the GI tract allowing enterohepatic circulation [13].

The mean $t_{½}$ for both regorafenib and M-2 is around 20–30 h; the $t_{½}$ for M-5 is around 50–60 h [12, 13]. Approximately 90 % of a radiolabeled dose of regorafenib (120 mg, oral solution) was recovered within 12 days of administration, with approximately 71 % of the dose excreted in the faeces (47 % as parent compound, 24 % as metabolites) and approximately 19 % of the dose excreted in urine (mainly as glucuronides) [12, 13]. Under steady-state conditions, excretion of glucuronides in the urine decreased to less than 10 % [13].

### 3.3 Special Populations

Age, gender or weight did not influence the pharmacokinetics of regorafenib to a clinically relevant extent [12, 13]. Mean systemic exposure of regorafenib was lower in Japanese patients [22] compared with exposure in European patients [19]; however, no dose adjustments are recommended.

No clinically relevant differences in the mean exposure of regorafenib, M-2 or M-5 were observed in patients with mild or moderate hepatic or renal impairment [12, 13]. Pharmacokinetic data for patients with severe hepatic or renal impairment are not yet available; however, a phase I study investigating the pharmacokinetics of regorafenib in severe renal impairment is underway (NCT01853046).

### 3.4 Drug Interactions

Given the metabolism of regorafenib in the liver by CYP isoenzymes, there is potential for drug interactions between regorafenib and other CYP substrates. In vitro, regorafenib, M-2 and M-5 inhibited the CYP isoenzymes CYP2C8, CYP2C9, CYP2B6, CYP3A4, CYP2C19 and CYP2D6 [12, 13]. In patients with advanced solid tumours, no clinically relevant change was observed in exposure to midazolam (CYP3A4 substrate), omeprazole (CYP2C19 substrate) or rosiglitazone (CYP2C8 substrate) when these drugs were coadministered with regorafenib; however, a 25 % increase was observed in the mean area under the concentration–time curve of warfarin (CYP2C9 substrate) [12, 13].

In studies in healthy volunteers, drug interactions have been observed between regorafenib and strong inducers or inhibitors of CYP3A4 [12, 13]. It is recommended that concomitant use of regorafenib with strong CYP3A4 inducers [e.g. rifampicin (rifampin), phenytoin, hypericum (St. John's wort)] or inhibitors (e.g. ketoconazole, clarithromycin, grapefruit juice) be avoided [12, 13].

In vitro, regorafenib and its metabolites competitively inhibited UGT1A1 and UGT1A9 at therapeutically

relevant concentrations, with limited clinical data also indicating that coadministration of regorafenib may increase systemic exposure to UGT1A1 and UGT1A9 substrates [12, 13]. Furthermore, in vitro, regorafenib and its major metabolites inhibited the transporters P-glycoprotein and breast cancer resistance protein [12, 13]. Finally, coadministration of bile salt-sequestering agents (e.g. colestyramine and colesevelam) or antibacterials affecting the GI microflora may interfere with the enterohepatic circulation of regorafenib or its metabolites, potentially resulting in decreased exposure [13].

## 4 Therapeutic Efficacy

This section focuses on the results of the pivotal phase III GRID trial that investigated the efficacy, safety and tolerability of regorafenib in patients with unresectable and/or metastatic GISTs, with previous failure of at least imatinib and sunitinib [14]. The potential for regorafenib in the treatment of advanced GISTs after failure of imatinib and sunitinib was earlier demonstrated in a phase II clinical trial in which 26/33 (79 %) patients achieved clinical benefit (four patients with partial response and 22 patients with stable disease lasting ≥16 weeks) while receiving regorafenib [24]. The regorafenib dosing schedule used in these two trials [and subsequently approved (Sect. 6)] was determined in an earlier phase I dose escalation trial in patients with advanced solid tumours [19].

The GRID trial was a randomized, double-blind, placebo-controlled, multinational trial conducted in patients ($n = 199$) with advanced refractory GIST [14]. In the trial, patients with histologically confirmed, metastatic or unresectable GIST, with previous failure of at least imatinib (because of progression or intolerance) and sunitinib (because of progression) were randomized to receive oral regorafenib 160 mg ($n = 133$) or placebo ($n = 66$) once daily for 21 days followed by 7 days off in repeating 28-day cycles. In addition, all patients received best supportive care. Double-blind administration of study drug was continued until disease progression, the occurrence of unacceptable toxic effects, or withdrawal of the patient from the trial. During the trial, the dose of study drug could be reduced or delayed in the event of unacceptable toxic effects. The median duration of treatment during the double-blind period was 22.9 weeks for the regorafenib arm and 7.0 weeks for the placebo arm. Following progression, treatment assignment was unblinded and, at the discretion of the investigator, patients in either arm were able to commence open-label regorafenib.

Baseline characteristics were well matched between the two treatment arms, although a numerically higher proportion of patients in the regorafenib group had received previous imatinib therapy for ≤18 months compared with the placebo group (33 vs. 17 %) [14]. The median age of patients was ≈60 years. All patients had adequate haematological, hepatic, renal and cardiac function, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

The primary endpoint of the trial was PFS per modified Response Evaluation Criteria In Solid Tumours 1.1, as assessed by blinded central radiology reviewers [14]. The final PFS analysis was performed when 144 PFS events were reached. Efficacy analyses were conducted in the intent-to-treat population; one patient in the regorafenib arm did not receive any study drug.

Regorafenib significantly improved PFS in patients with metastatic or unresectable GIST after failure of prior treatment with at least imatinib and sunitinib [14]. Regorafenib significantly prolonged median PFS by 3.9 months relative to placebo, corresponding to a 73 % reduction in the risk of progression or death (Table 1). At 3 months, the PFS rates were 60 and 11 % for the regorafenib and placebo groups, respectively; at 6 months they were 38 and 0 %. Following progression, 56 placebo recipients (85 %) crossed over to receive open-label regorafenib. Among these patients, median PFS (assessed by investigator rather than central review) was 5.0 months [14].

A significant improvement in PFS in regorafenib versus placebo recipients was also observed in patients stratified according to previous systemic anticancer treatment [two lines (HR 0.23; 95 % CI 0.14–0.37) or three or more lines (HR 0.31; 95 % CI 0.18–0.54)] and geographical region [Asia (HR 0.30; 95 % CI 0.15–0.62) or rest of the world (HR 0.24; 95 % CI 0.16–0.37)] [14]. The benefit of regorafenib in improving PFS was also consistent across several other prespecified subgroups, including sex (male or female), age (<65 or ≥65 years), region (North America or outside North America), body mass index (<25, 25 to <30 or ≥30 kg/m$^2$), ECOG score (0 or 1), *KIT* mutation biomarker (exon 9 or exon 11 mutation) and duration of imatinib treatment (≥6 to <18 or ≥18 months) [HRs ranging from 0.15 to 0.42]; in the subgroup of patients who received imatinib for <6 months ($n = 22$), the improvement in PFS was not significant (HR 0.50; 95 % CI 0.17–1.73) [14]. A post hoc subgroup analysis in Japanese patients also suggested a PFS benefit with regorafenib, as indicated by a significantly ($p = 0.0002$) longer PFS duration in regorafenib than placebo recipients [7.1 vs. 0.9 months; HR 0.08; 95 % CI 0.02–0.45] ($n = 12$ and 5 in the respective groups) [26].

Regorafenib treatment was also associated with a significant improvement in the disease control rate compared with placebo (Table 1) [14]. Although there were no cases of complete response in either group, and stable disease was the best response for the vast majority of patients with disease control, the disease control rate was significantly higher (approximately sixfold) in the regorafenib group compared with

**Table 1** Efficacy of regorafenib in GIST patients in the GRID trial [14, 25]

| Outcomes | REG ($n = 133$) | PL ($n = 66$) | HR (95 % CI) |
|---|---|---|---|
| Median PFS (months)[a,b] | 4.8 | 0.9 | 0.27 (0.19–0.39)* |
| Median OS (months)[b] | 17.4 | 17.4 | 0.85 (0.60–1.21)[c] |
| | | | 0.39 (0.26–0.58)[d] |
| | | | 0.51 (0.35–0.73)[e] |
| Disease control rate (%)[f] | 52.6* | 9.1 | NA |

Results are for PFS and disease control rate assessed at the time of final PFS analysis (data cutoff 26 January 2012) and OS assessed in an updated analysis (data cutoff 31 January 2014)

*HR* hazard ratio, *NA* not available, *OS* overall survival, *PFS* progression-free survival, *PL* placebo, *REG* regorafenib

* $p < 0.0001$ versus PL

[a] Primary endpoint

[b] Based on Kaplan–Meier estimates

[c] Intent-to-treat population (uncorrected analysis)

[d] Analysis corrected for crossover using rank preserving structural failure time method

[e] Analysis corrected for crossover using iterative parameter estimation method

[f] Disease control rate defined as the rate of complete response or partial response or stable disease lasting ≥12 weeks

the placebo group (Table 1). The overall response rate was 4.5 % in regorafenib recipients and 1.5 % in placebo recipients (all responses were partial responses) [14].

No significant difference in OS was observed between regorafenib and placebo recipients in either a preplanned interim analysis conducted at the time of the final PFS analysis (29 [22 %] vs. 17 [26 %] events; HR 0.77; 95 % CI 0.42–1.41; $p = 0.199$) [14] or in an updated analysis conducted 2 years later (91 [68 %] vs. 48 [73 %] events; HR 0.85; 95 % CI 0.60–1.21; $p = 0.180$) (Table 1) [21, 25]. However, it should be noted that the ability of patients in the placebo arm to cross over to regorafenib following disease progression likely confounded the OS results (with 94.5 % of all patients receiving regorafenib in either the double-blind or open-label periods of the trial). An exploratory OS analysis correcting for the impact of the cross-over (reported as an abstract) suggested there may be a survival benefit associated with regorafenib treatment (Table 1) [25].

Finally, exploratory health-related quality of life (HR-QoL) analyses (reported in an abstract) suggested that HR-QoL was similar across patients in the GRID trial regorafenib and placebo arms [27].

## 5 Tolerability

### 5.1 In GIST Patients in the GRID Trial

Regorafenib had an acceptable tolerability profile in patients with GIST in the GRID trial [14]. Moreover, the tolerability profile from the trial was consistent with the profile derived from earlier regorafenib clinical trials [24, 28] and consistent with profiles for other drugs having a similar target spectrum [29, 30]. The most commonly reported drug-related adverse events in the trial were hand-foot skin reaction (HFSR), hypertension, diarrhoea and fatigue (Fig. 1) [14].

Overall, drug-related adverse events were reported in 98 % of regorafenib recipients and 68 % of placebo recipients during double-blind treatment [14]. The incidence of drug-related adverse events of grade ≥3 severity was 61 % in the regorafenib arm versus 14 % in the placebo arm, with the most common regorafenib-related adverse events of grade ≥3 severity being hypertension (23 %), HFSR (20 %) and diarrhoea (5 %). Grade 5 adverse events (deaths) were reported for 5 % of patients in each group, seven patients in the regorafenib arm and three patients in the placebo arm [14]. Two of the grade 5 adverse events in the regorafenib arm (cardiac arrest and hepatic failure) and one of the events in the placebo arm (fatigue) were deemed to be drug-related. Twenty-nine percent of patients in the regorafenib arm experienced serious adverse events (SAEs) compared with 21 % of patients in the placebo arm [14]. The most common SAEs in regorafenib recipients were abdominal pain (4 %), fever (2 %) and dehydration (2 %) and in placebo recipients were fatigue and pain (both 3 %). Although dose modifications because of adverse events (based on a prespecified schedule) were reported for 72 % of patients in the regorafenib arm versus 26 % of patients in the placebo arm, the incidence of adverse events leading to permanent discontinuation of treatment was 6 and 8 % in the corresponding groups, indicating that adverse events were generally manageable with dose modification [14].

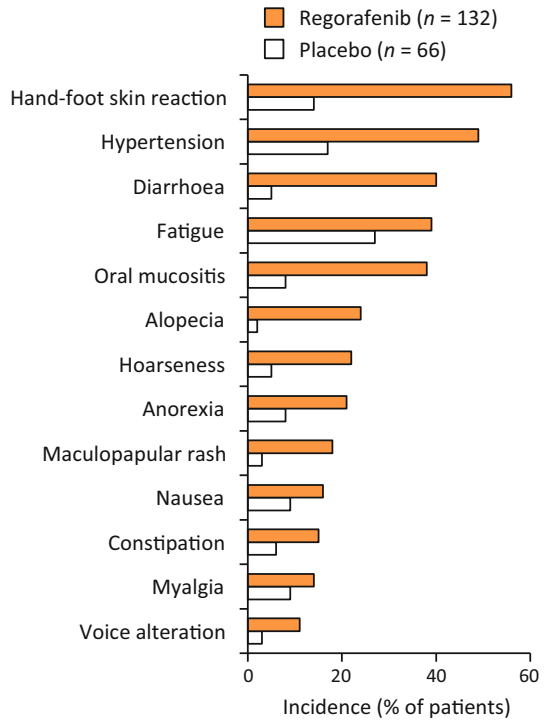


**Fig. 1** Incidence of drug-related adverse events in the GRID trial [14]. Adverse events shown are all-grade adverse events reported in ≥10 % of patients during the double-blind treatment period of the trial

#### *5.1.1 In Japanese Patients*

Overall, the tolerability profile of regorafenib in Japanese patients in the GRID trial ($n = 17$) was consistent with that observed in the full study population [26]. However, some regorafenib-related adverse events [e.g. HFSR (92 vs. 56 %) and maculopapular rash (50 vs. 18 %)], as well as regorafenib-related adverse events of grade ≥3 severity (83 vs. 61 %), were reported by a numerically higher proportion of Japanese regorafenib recipients ($n = 12$) compared with regorafenib recipients in the overall study population ($n = 132$) [26].

### 5.2 Specific Adverse Events

Regorafenib has been associated with a risk of hepatotoxicity [12, 13]. A numerically higher incidence of liver function test abnormalities has been observed in patients receiving regorafenib compared with patients receiving placebo, although the abnormalities are mostly of grade 1 or 2 severity [12, 13]. Three cases of fatal drug-induced liver injury have been reported in >1200 patients who received regorafenib across several clinical trials; in two of the cases, the patients had liver metastases [12, 13]. The US prescribing information for regorafenib carries a boxed warning for severe and sometimes fatal hepatotoxicity [12].

Regorafenib has been associated with an increased incidence of dermatological toxicity [12, 13]. In the GRID trial, drug-related HFSR was reported in 56 % of patients receiving regorafenib compared with 14 % of patients receiving placebo [14]. The majority (71 %) of cases of HFSR appeared during the first cycle of regorafenib treatment [12, 13]. In the same trial, drug-related maculopapular rash and alopecia were also reported in 18 and 24 % of patients receiving regorafenib (Fig. 1) [14]. Drug-related maculopapular rash of grade 3 severity was reported in 2 % of regorafenib recipients versus 0 % of placebo recipients; no episodes of grade 4 severity were reported [14]. Incidents of other serious skin adverse events, including erythema multiforme, Stevens Johnson Syndrome and toxic epidermal necrosis, have also been reported in patients receiving regorafenib in clinical trials [12].

Hypertension is an adverse event commonly associated with antiangiogenic agents such as regorafenib. In the GRID trial, drug-related hypertension was reported in 49 % of patients in the regorafenib arm versus 17 % of patients in the placebo arm [14]. Similar to HFSR, the onset of hypertension occurred in the first cycle of treatment in the majority of cases [12, 13]. Hypertensive crisis was reported in 0.25 % of regorafenib recipients across several clinical trials [12]. It should be noted that patients with uncontrolled hypertension were excluded from the GRID trial [14].

There have been occurrences of haemorrhage during regorafenib therapy, including fatal events [12, 13]. In the GRID trial, haemorrhage was reported as an adverse event in 11 % of patients in the regorafenib arm compared with 3 % of patients in the placebo arm [12]. Incidents of GI perforation or fistula have also been reported in patients receiving regorafenib, including fatal events [12, 13]. In the GRID trial, 2.1 % of patients who received regorafenib in either the double-blind or open-label periods of the trial developed GI perforation or fistula, including two cases of fatal GI perforation [12]. However, it should be noted that GI perforation or fistula are common disease-related complications in patients with intra-abdominal malignancies [13].

Other laboratory abnormalities have also been observed in patients receiving regorafenib, including biochemical, metabolic and haematological abnormalities [12, 13]. The abnormalities are not usually associated with clinical manifestations. However, it is recommended that laboratory parameters be monitored during regorafenib treatment.

Regorafenib has been associated with an increased incidence of myocardial ischaemia and infarction, as well as with an increased risk of infection [12, 13]. Patients with unstable angina, recent myocardial infarction or congestive heart failure of at least New York Heart Association class 2

severity were excluded from the GRID trial [14]. Finally, one case of posterior reversible encephalopathy syndrome has been reported among >1200 patients who received regorafenib across several clinical trials [12, 13].

## 6 Dosage and Administration

Regorafenib is indicated in the treatment of patients with locally advanced, unresectable or metastatic GISTs who have previously been treated with imatinib and sunitinib [12, 13, 23]. Under the EU and Canadian approvals, it is specified that regorafenib is approved in adult patients who have had disease progression on or intolerance to imatinib and sunitinib treatment [13, 23].

The recommended dose of regorafenib is 160 mg (four 40 mg tablets) taken orally once daily for the first 21 days of each 28-day cycle [12, 13, 23]. Regorafenib should be taken at the same time each day with a light, low-fat (<30 %) meal. Treatment should be continued until disease progression or unacceptable toxicity occurs. Dose modifications or interruptions may be required based on individual safety and tolerability considerations.

Local prescribing information should be consulted for full details regarding the administration of regorafenib, including further information on associated warnings and precautions and dosage adjustments to manage adverse events.

## 7 Current Status of Regorafenib in the Management of GIST

The development of tyrosine kinase inhibitors has had a significant impact on the treatment of advanced GISTs. While imatinib and sunitinib remain the first- and second-line therapies, respectively, for the treatment of unresectable and/or metastatic GISTs, the vast majority of advanced GISTs will become resistant to these agents, typically within a few years. Until the approval of regorafenib, third-line treatment options for advanced GISTs were very limited.

The efficacy of regorafenib in the treatment of advanced GISTs was demonstrated in the pivotal phase III GRID trial which showed that, compared with placebo, regorafenib was associated with a 73 % reduction in the risk of disease progression or death, as well as with a significant improvement in disease control (Sect. 4). The ability of regorafenib to significantly prolong PFS is a promising finding, especially given the previous treatment of patients in the GRID trial—all patients in the trial had previously received at least imatinib and sunitinib, and 43 % had received at least one other systemic anticancer treatment [14]. Moreover, exploratory HR-QoL analyses suggested that the improvement in PFS under regorafenib treatment compared with placebo was achieved while maintaining a comparable HR-QoL [27].

No benefit of regorafenib in prolonging OS was demonstrated in the GRID trial (Sect. 4). However, the ability of placebo patients to cross over to regorafenib following progression likely confounded the OS results. An exploratory analysis correcting for the impact of the cross-over on OS in the trial suggested there may be a survival benefit associated with regorafenib treatment [25]. Moreover, although it is not possible to directly compare data across different trials, a median OS of 17.4 months (updated analysis) in regorafenib recipients in the GRID trial is considerably longer than what has commonly been observed in other studies in GIST patients previously treated with imatinib and sunitinib, where median OS has typically been less than 12 months [21].

Regorafenib has an acceptable tolerability profile (Sect. 5). The most commonly reported drug-related adverse events in the GRID trial were HFSR, hypertension, diarrhoea and fatigue, consistent with established profiles for tyrosine kinase inhibitors with similar target spectra. Adverse events such as HFSR and hypertension commonly appeared during the first cycle of regorafenib treatment and were generally manageable with dose modification. Adverse events may also be moderated through preventative and/or supportive measures. For example, the protection of pressure points on the feet and the use of creams and emollients may help to prevent or alleviate symptoms of HFSR [31].

The approval of regorafenib for advanced GISTs following failure of imatinib and sunitinib has added a valuable new treatment option for this complex disease. Current National Comprehensive Cancer Network® (NCCN) and European Society for Medical Oncology (ESMO) guidelines both recommend regorafenib as third-line treatment for unresectable and/or metastatic GISTs [3, 4]. Following failure of all standard approved therapies, there is some evidence that continuing tyrosine kinase inhibitor therapy may be beneficial [3, 4]. In patients with advanced GISTs rechallenged with imatinib following previous failure of imatinib and sunitinib in the phase III RIGHT clinical trial, a statistically significant ($p = 0.005$ vs. placebo) albeit small (0.9 months) improvement in median PFS was observed [32]. Clinical experience has also suggested that continued treatment with a tyrosine kinase inhibitor, even in the setting of progressive disease, may slow down (or at least prevent acceleration of) further progression [3, 4]. A phase Ib trial (SURE) investigating the use of alternating sunitinib and regorafenib following failure of the standard approved therapies (imatinib, sunitinib and regorafenib) is currently underway (NCT02164240).

Besides specific treatments, NCCN and ESMO guidelines strongly recommend routine mutational analysis [3, 4]. GISTs represent a complex disease where a variety of mutations can be found in different tumours [1, 2], and the response of patients to different tyrosine kinase inhibitors can depend on the specific mutation(s) within the GISTs [3, 7]. Individualized disease management strategies are likely to be beneficial, and this will be an important area of focus for future studies [30, 33].

In conclusion, regorafenib significantly prolongs PFS and has a generally acceptable tolerability profile in patients with advanced GISTs following failure of imatinib and sunitinib. Thus, regorafenib presents a valuable new tool in the treatment of this population where treatment options were previously very limited.

**Data selection sources:** Relevant medical literature (including published and unpublished data) on regorafenib was identified by searching databases including MEDLINE (from 1946), PubMed (from 1946) and EMBASE (from 1996) [searches last updated 13 April 2015], bibliographies from published literature, clinical trial registries/databases and websites. Additional information was also requested from the company developing the drug.
**Search terms:** Regorafenib, Stivarga, BAY 73-4506.
**Study selection:** Studies in patients with gastrointestinal stromal tumours who received regorafenib. When available, large, well designed, comparative trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

**Disclosure** The preparation of this review was not supported by any external funding. During the peer review process, the manufacturer of the agent under review was offered an opportunity to comment on this article. Changes resulting from comments received were made by the authors on the basis of scientific and editorial merit. Matt Shirley and Gillian Keating are salaried employees of Adis/Springer.

## References

1. Iorio N, Sawaya RA, Friedenberg FK. Review article: the biology, diagnosis and management of gastrointestinal stromal tumours. Aliment Pharmacol Ther. 2014;39(12):1376–86.
2. Miettinen M, Lasota J. Gastrointestinal stromal tumors. Gastroenterol Clin North Am. 2013;42(2):399–415.
3. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology (NCCN Guideline®): soft tissue sarcoma (Version 1.2015). 2015. http://www.nccn.org. Accessed 13 Apr 2015.
4. ESMO/European Sarcoma Network Working Group. Gastrointestinal stromal tumours: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014;25(Suppl 3):321–6.
5. Vadakara J, von Mehren M. Gastrointestinal stromal tumors: management of metastatic disease and emerging therapies. Hematol Oncol Clin North Am. 2013;27(5):905–20.
6. Serrano C, George S. Recent advances in the treatment of gastrointestinal stromal tumors. Ther Adv Med Oncol. 2014;6(3):115–27.
7. Hirota S, Isozaki K. Pathology of gastrointestinal stromal tumors. Pathol Int. 2006;56(1):1–9.
8. Siddiqui MAA, Scott LJ. Imatinib: a review of its use in the management of gastrointestinal stromal tumours. Drugs. 2007;67(5):805–20.
9. Deeks ED, Keating GM. Sunitinib. Drugs. 2006;66(17):2255–66.
10. Demetri GD, van Oosterom AT, Garrett CR, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. Lancet. 2006;368(9544):1329–38.
11. Guo T, Hajdu M, Agaram NP, et al. Mechanisms of sunitinib resistance in gastrointestinal stromal tumors harboring $KIT^{AY502-3ins}$ mutation: an in vitro mutagenesis screen for drug resistance. Clin Cancer Res. 2009;15(22):6862–70.
12. US FDA. Stivarga (regorafenib): prescribing information. 2015. http://www.fda.gov. Accessed 20 Apr 2015.
13. European Medicines Agency. Stivarga: summary of product characteristics. 2015. http://www.ema.europa.eu. Accessed 30 Mar 2015.
14. Demetri GD, Reichardt P, Kang Y-K, et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet. 2013;381(9863):295–302.
15. Wilhelm SM, Dumas J, Adnane L, et al. Regorafenib (BAY 73-4506): a new oral multikinase inhibitor of angiogenic, stromal and oncogenic receptor tyrosine kinases with potent preclinical antitumor activity. Int J Cancer. 2011;129(1):245–55.
16. Schmieder R, Hoffmann J, Becker M, et al. Regorafenib (BAY 73-4506): antitumor and antimetastatic activities in preclinical models of colorectal cancer. Int J Cancer. 2014;135(6):1487–96.
17. Van Looy T, Gebreyohannes YK, Wozniak A, et al. Characterization and assessment of the sensitivity and resistance of a newly established human gastrointestinal stromal tumour xenograft model to treatment with tyrosine kinase inhibitors. Clin Sarcoma Res. 2014;4:10.
18. Abou-Elkacem L, Arns S, Brix G, et al. Regorafenib inhibits growth, angiogenesis, and metastasis in a highly aggressive, orthotopic colon cancer model. Mol Cancer Ther. 2013;12(7):1322–31.
19. Mross K, Frost A, Steinbild S, et al. A phase I dose-escalation study of regorafenib (BAY 73-4506), an inhibitor of oncogenic, angiogenic, and stromal kinases, in patients with advanced solid tumors. Clin Cancer Res. 2012;18(9):2658–67.
20. Strumberg D, Scheulen ME, Schultheis B, et al. Regorafenib (BAY 73-4506) in advanced colorectal cancer: a phase I study. Br J Cancer. 2012;106(11):1722–7.
21. European Medicines Agency. Stivarga: CHMP extension of indication variation assessment report. 2014. http://www.ema.europa.eu. Accessed 30 Mar 2015.
22. Sunakawa Y, Furuse J, Okusaka T, et al. Regorafenib in Japanese patients with solid tumors: phase I study of safety, efficacy, and pharmacokinetics. Invest New Drugs. 2014;32(1):104–12.
23. Health Canada. Stivarga (regorafenib tablets): product monograph. 2015. http://webprod5.hc-sc.gc.ca/dpd-bdpp/start-debuter.do?lang=eng. Accessed 30 Mar 2015.
24. George S, Wang Q, Heinrich MC, et al. Efficacy and safety of regorafenib in patients with metastatic and/or unresectable GI stromal tumor after failure of imatinib and sunitinib: a multicenter phase II trial. J Clin Oncol. 2012;30(19):2401–7.
25. Demetri GD, Reichardt P, Kang Y-K, et al. An updated overall survival analysis with correction for protocol-planned crossover of the international, phase III, randomized, placebo-controlled trial of regorafenib in advanced gastrointestinal stromal tumors after failure of imatinib and sunitinib (GRID) [abstract no. 110]. In: 2015 Gastrointestinal Cancers Symposium. 2015.

26. Komatsu Y, Doi T, Sawaki A, et al. Regorafenib for advanced gastrointestinal stromal tumors following imatinib and sunitinib treatment: a subgroup analysis evaluating Japanese patients in the phase III GRID trial. Int J Clin Oncol. 2015. doi:10.1007/s10147-015-0790-y.
27. Chang J, Casali PG, Reichardt P, et al. Health-related quality of life (HRQoL) of patients with advanced gastrointestinal stromal tumors (GIST) treated with regorafenib (REG) vs placebo (P) in the phase III GRID trial [abstract no. 3830]. In: The European Cancer Congress. 2013.
28. Grothey A, Van Cutsem E, Sobrero A, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet. 2013;381(9863):303–12.
29. Hartmann JT, Haap M, Kopp H-G, et al. Tyrosine kinase inhibitors—a review on pharmacology, metabolism and side effects. Curr Drug Metab. 2009;10(5):470–81.
30. Strumberg D, Schultheis B. Regorafenib for cancer. Expert Opin Investig Drugs. 2012;21(6):879–89.
31. Grothey A, George S, van Cutsem E, et al. Optimizing treatment outcomes with regorafenib: personalized dosing and other strategies to support patient care. Oncologist. 2014;19(6):669–80.
32. Kang Y-K, Ryu M-H, Yoo C, et al. Resumption of imatinib to control metastatic or unresectable gastrointestinal stromal tumours after failure of imatinib and sunitinib (RIGHT): a randomised, placebo-controlled, phase 3 trial. Lancet Oncol. 2013;14(12):1175–82.
33. Yip D, Zalcberg J, Ackland S, et al. Controversies in the management of gastrointestinal stromal tumors. Asia Pac J Clin Oncol. 2014;10(3):216–27.