Regorafenib

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Abstract

Regorafenib (BAY 73-4506, Stivarga®) is an oral diphenylurea multi-kinase inhibitor that targets angiogenic (VEGFR1-3, TIE2), stromal (PDGFR-β, FGFR), and oncogenic receptor tyrosine kinases (KIT, RET, and RAF). Regorafenib is the first small-molecule multi-kinase inhibitor to achieve survival benefits in metastatic colorectal cancer that has progressed after all standard therapies. Consequently, Regorafenib was FDA approved for this indication in 2012. In addition, Regorafenib treatment resulted in a significant improvement in progression-free survival (PFS) compared to placebo in patients with metastatic gastrointestinal stromal tumors (GIST) after progression on standard treatments and is also FDA-approved in this indication since 2013. In 2017, Regorafenib has been FDA approved for the treatment of patients with advanced hepatocellular carcinoma (HCC) previously treated with Sorafenib. In this situation, Regorafenib significantly improved PFS and overall survival (OS) compared to placebo. Regorafenib has also been examined in several clinical trials (mostly phase II) in different tumor entities, including renal cell carcinoma (RCC), soft-tissue sarcoma (STS), and additional phase II trials ongoing (e.g., second- and third-line treatment for medullary thyroid cancer, NCT02657551).

Keywords

Regorafenib · CRC · HCC · GIST · TKI

1 Structure, Mechanism of Action, and Pharmacokinetics

1.1 Mechanism of Action

Regorafenib (see Fig. 1) is a small-molecule inhibitor of various membrane-bound and intracellular kinases involved in normal cellular functions as well as pathologic processes, such as oncogenesis, tumor angiogenesis, and maintenance of the tumor microenvironment. In biochemical in vitro or cell-based assays, Regorafenib or its major human active metabolites M-2 and M-5 inhibited the activity of RET, VEGFR 1-3, KIT, PDGFR-alpha, PDGFR-beta, FGFR1, FGFR2, TIE2, DDR2, TrkA, Eph2A, RAF-1, BRAF, BRAFV600E, SAPK2, PTK5, and Abl at concentrations that can be achieved clinically.

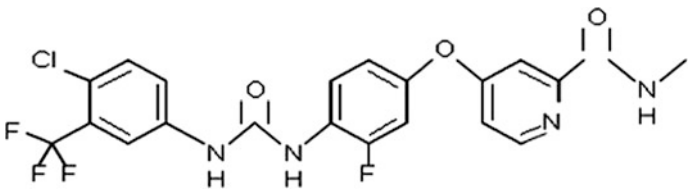

Fig. 1 Chemical structure of Regorafenib

1.2 Pharmacokinetics and Elimination

The standard dose of Regorafenib is 160 mg taken orally once daily as tablets. The mean relative bioavailability of orally taken Regorafenib is 69%. Regorafenib undergoes enterohepatic circulation with multiple plasma concentration peaks observed across the 24-h dosing interval. Regorafenib is highly bound (99.5%) to human plasma proteins and metabolized by CYP3A4 and UGT1A9. The main circulating metabolites of Regorafenib in human plasma are M-2 (*N*-oxide) and M-5 (*N*-oxide and *N*-desmethyl). Both metabolites have similar in vitro pharmacological activity and are highly protein bound (>99.0%). The elimination half-life for Regorafenib and its M-2 metabolite in plasma are 28 and 25 h, respectively. M-5 has a longer elimination half-life of 51 h. Approximately, 71% of a radiolabeled dose of Regorafenib is excreted via feces and 19% of the dose is excreted via urine. Based on a population pharmacokinetic analysis, there is no clinically relevant effect of age, gender, or weight on the pharmacokinetics of Regorafenib.

1.3 Regorafenib in Renal or Hepatic Impairment

Because of its major elimination via feces, no differences in the mean steady-state exposure to Regorafenib, its M-2 or M-5 metabolites were observed in patients with mild renal impairment compared to patients with normal renal function. There are no clinical data for patients with severe renal impairment or end-stage renal disease. There were no clinically important differences observed in the mean exposure to Regorafenib, M-2, or M-5 in patients with mild or moderate hepatic impairment (Child-Pugh A and B) compared to the patients with normal hepatic function. There are no clinical data for patients with severe hepatic impairment (Child-Pugh C).

2 Preclinical Data

Regorafenib is a multitarget small-molecule compound with potent activity against a number of angiogenic and stromal TKs (tyrosine kinases), including VEGFR-2, TIE2, FGFR-1, and the PDGFR. Regorafenib also blocks KIT, RET, wild-type, and V600 mutant BRAF. An antiangiogenic effect of Regorafenib was demonstrated

in vivo by dynamic contrast-enhanced magnetic resonance imaging. Regorafenib administered once orally at 10 mg/kg significantly decreased the extravasation of Gadomer, an intravascular macromolecular MRI contrast agent, in the vasculature of rat GS9L glioblastoma tumor xenografts (Wilhelm et al. 2011). In a daily dosing study, the pharmacodynamic effects persisted for 48 h after the last dosing and correlated with tumor growth inhibition (TGI). A significant reduction in the tumor microvessel area was observed in a human colorectal xenograft after daily dosing at 10 and 30 mg/kg.

Regorafenib exhibited potent dose-dependent TGI in various preclinical human xenograft models in mice with tumor shrinkage observed in breast MDA-MB-231 and renal 786-O carcinoma models (Wilhelm et al. 2011). Pharmacodynamic analyses of the breast cancer model revealed a strong reduction in Ki-67 immunoreactivity (a proliferation marker) and phosphorylation/activation of ERK 1/2.

Various low concentrations of Regorafenib were examined in vitro in two human HCC cell lines with respect to its effects on alpha-fetoprotein (AFP) levels, cell growth, migration, and invasion (Carr et al. 2013). AFP secretion was inhibited at 0.1–1 μM Regorafenib. Cell migration and invasion were inhibited at similar drug concentrations. Interestingly, a 10-fold higher drug concentration was required to inhibit cell growth in both AFP-positive and AFP-negative cell lines (Carr et al. 2013). These data demonstrate that Regorafenib is an active multi-kinase inhibitor with a distinct target profile.

3 Clinical Data

3.1 Regorafenib in Metastatic Colorectal Cancer (mCRC)

There are limited treatment options available for patients with metastatic colorectal cancer progressing after all approved standard therapies. However, many patients maintain a good performance status and are eligible for further therapy. An international phase III trial, the CORRECT trial (Grothey et al. 2013), was performed to assess Regorafenib in patients with mCRC progressing after all approved standard therapies. 760 patients with a good performance status (ECOG 0 and 1) were randomized in a 2:1 ratio to receive Regorafenib (n = 505) or placebo (n = 255), respectively. The primary endpoint of overall survival was met at a preplanned interim analysis. The median overall survival was 6.4 months in the Regorafenib group versus 5.0 months in the placebo group (hazard ratio 0.77; 95% CI 0.64–0.94; one-sided p = 0.0052). Treatment-related adverse events occurred in 465 (93%) patients assigned to Regorafenib and in 154 (61%) of those assigned to placebo. The most common adverse events of grade 3 or higher related to Regorafenib were hand–foot skin reaction (83 patients, 17%), fatigue (48, 10%), diarrhea (36, 7%), hypertension (36, 7%), and rash or desquamation (29, 6%). Thus, Regorafenib is the first small-molecule multi-kinase inhibitor with survival benefits

Table 1 Results from the CORRECT trial (Grothey et al. 2013) in patients with colorectal cancer

	Regorafenib (n = 500)	Placebo (n = 253)	
mOS (month)	6.4	5.0	HR 0.77; 95% CI 0.64–0.94; p = 0.0052
mPFS (month)	1.9	1.7	HR 0.49, 95% CI 0.42–0.58, p < 0.0001
CR	0	0	
PR	4%	1%	(p = 0.19)
DCR	41%	15%	(p < 0.0001), 6 weeks after randomization

mOS Median overall survival, *mPFS* progression-free survival, *HR* hazard ratio, *CI* confidence interval, *CR* complete remission, *PR* partial remission, *DCR* disease control rate

in mCRC progressing after all standard therapies. The FDA approved the use of Regorafenib for this indication in September 2012 (Table 1).

The combination of Regorafenib with FOLFOX or FOLFIRI as first- or second-line treatment of mCRC was tested in a multicenter, phase Ib study (Schultheis et al. 2013) with 45 patients. Safety and pharmacokinetics were the primary objectives, and tumor response was the secondary objective. Patients were treated every 2 weeks with mFOLFOX 6 or FOLFIRI. On days 4–10, patients received Regorafenib 160 mg orally once daily. The median duration of treatment was 108 days (range 2–345 days). Treatment was stopped for adverse events or death (17 patients), disease progression (11 patients), and withdrawal of consent or by investigators decision (11 patients). Drug-related adverse events occurred in 44 patients ($\geq$ grade 3 in 32 patients: mostly neutropenia and leukopenia, hand–foot skin reaction, and hypophosphatemia). Thirty-three patients achieved disease control (partial response or stable disease) for a median of 126 days (range 42–281 days). With 71% $\geq$ grade 3 toxicity in this small study, Regorafenib exhibited a not ideal tolerability in this setting. Another phase II trial examining mFOLFOX6 in combination with Regorafenib as first-line treatment of mCRC failed its primary endpoint and showed no difference in the response rate compared to historical controls (Argiles et al. 2015).

In the second-line setting, a phase II trial examined Regorafenib (R) in combination with FOLFIRI (F) versus Placebo (P) + FOLFIRI (O'Neil et al. 2016). 181 patients were enrolled, and 62.5% had prior anti-VEGF treatment. Median PFS was 6.14 months for the combination of F plus R versus 5.29 months for F plus P (HR 0.69, log-rank p = 0.02). Median OS was 13.2 months and 12 months, and RR was 32% versus 19% for F plus R versus F plus P, respectively (HR 1.06, p = 0.76). Thus, Regorafenib in combination with FOLFIRI could improve PFS compared to FOLFIRI alone in this setting. The higher efficacy has to be balanced against a higher toxicity: There was more grade $\geq$ 3 neutropenia, diarrhea, hypophosphatemia, fatigue, HTN, and hand–foot syndrome in the F + R group (Table 2).

Table 2 Toxicity data (adverse events: CTC Grades 3 and 4) taken from the CORRECT trial (phase III) (Grothey et al. 2013)

Event	Regorafenib (n = 500)		Placebo (n = 253)	
	Grade 3	Grade 4	Grade 3	Grade 4
Any event	51%	3%	12%	2%
Fatique	9%	<1%	5%	<1%
Hand–foot skin reaction	17%	0	<1%	0
Diarrhea	7%	<1%	1%	0
Anorexia	3%	0	3%	0
Voice changes	<1%	0	0	0
Hypertension	7%	0	1%	0
Oral mucositis	3%	0	0	0
Rash or desquamation	6%	0	0	0
Nausea	<1%	0	0	0
Fever	1%	0	0	0
Vomiting	1%	0	0	0
Sensory neuropathy	<1%	0	0	0
Muscle pain	<1%	0	<1%	0
Headache	1%	0	0	0
Pain, abdomen	<1%	0	0	0
Laboratory event				
Thrombocytopenia	3%	<1%	<1%	0
Hyperbilirubinaemia	2%	0	1%	0
Proteinuria	1%	0	<1%	0
Anemia	2%	<1%	0	0
Hypophosphatemia	4%	0	<1%	0

3.2 Regorafenib in Metastatic Gastrointestinal Stromal Tumors (mGIST)

Metastatic GIST is a life-threatening disease with no therapy of proven efficacy after failure of imatinib and sunitinib. Mutant KIT and PDGFR-alpha, both Regorafenib targets, remain dominant oncogenic drivers in GIST refractory to imatinib and sunitinib. Efficacy and safety of Regorafenib were evaluated in a multicenter, single-arm phase II trial (n = 34) of Regorafenib in patients with advanced GIST after failure of imatinib and sunitinib (George et al. 2012). This trial revealed positive results for Regorafenib with respect to tumor control. Consequently, the GRID trial, an international, multicenter, randomized, double-blind, placebo-controlled phase III trial in unresectable, locally advanced, or metastatic GIST, who had been previously treated with imatinib and sunitinib, was initiated (Demetri et al. 2013).

The primary outcome measure in this trial was progression-free survival (PFS) based on disease assessment by independent radiological review using the

modified RECIST 1.1 criteria. In modified RECIST, lymph nodes and bone lesions are not counted as target lesions and a progressively growing new tumor nodule within a pre-existing tumor mass is classified as progression. The key secondary outcome measure was overall survival.

199 patients were randomized 2:1 to receive Regorafenib (n = 133) or placebo (n = 66), respectively. Median PFS per independent blinded central review was 4.8 months (IQR 1.4–9.2) for Regorafenib and 0.9 months (0.9–1.8) for placebo (hazard ratio [HR] 0.27, 95% CI 0.19–0.39; $p < 0.0001$). Upon progression, 56 patients (85%) assigned to placebo crossed over to Regorafenib. Drug-related adverse events were reported in 130 (98%) patients assigned to Regorafenib and 45 (68%) patients assigned to placebo. The most common Regorafenib-related adverse events of grade 3 or higher were hypertension (31 of 132, 23%), hand–foot skin reaction (26 of 132, 20%) and diarrhea (seven of 132, 5%).

Thus, oral Regorafenib significantly improves PFS compared to placebo in patients with metastatic GIST after progression on standard treatments. These results led to the approval of Regorafenib for this indication by the FDA in February 2013.

3.3 Regorafenib in Hepatocellular Carcinoma (HCC)

In 2017, Regorafenib has been approved by the FDA for the treatment of patients with advanced HCC who progressed on Sorafenib. This decision was based on the final data of the RESOURCE-trial (Bruix et al. 2017), a randomized, double-blind, placebo-controlled, multicenter phase III study of Regorafenib in patients with Child-Pugh A liver cirrhosis (maximum) and Barcelona Clinic Liver Cancer staging system (BCLC) Stage B or C HCC with documented disease progression following Sorafenib. Primary endpoint of the study was mOS. 573 patients were randomly assigned in a 2:1 ratio to Regorafenib or placebo (Regorafenib 160 mg orally once daily plus best supportive care (BSC) or matching placebo plus BSC for the first 21 days of each 28-day cycle). Treatment was continued until disease progression or unacceptable toxicity. The trial demonstrated a statistically significant improvement in OS (10.6 versus 7.8 months, HR = 0.63, $p < 0.0001$) and PFS (3.1 and 1.5 months, HR = 0.46, $p < 0.0001$) in favor for the Regorafenib arm. The overall response rate, based on modified RECIST, was 11% versus 4% in favor of regorafenib. Toxicity and safety were similar to other phase III trials with Regorafenib. The data showed that Regorafenib has acceptable tolerability and evidence of antitumor activity as single agent in patients with intermediate or advanced HCC that progressed following first-line Sorafenib.

3.4 Regorafenib in Metastatic Renal Cell Carcinoma (RCC)

Regorafenib inhibits VEGF receptors 1, 2, and 3 and PDGF receptors like other antiangiogenic tyrosine kinase inhibitors approved for treatment of advanced renal

cell cancer. Regorafenib also inhibits other potentially important angiogenic kinases like TIE2, activation of which is thought to be important in tumor escape mechanisms.

A phase II, open-label, non-randomized study assessed the safety and efficacy of the multi-kinase inhibitor Regorafenib for the treatment of renal cell carcinoma (Eisen et al. 2012). Patients with previously untreated metastatic or unresectable clear cell renal cell carcinoma received oral Regorafenib (160 mg per day) in cycles of 3 weeks on and 1 week off until disease progression. The primary efficacy endpoint was the proportion of patients who achieved an objective overall response. 49 patients received Regorafenib. The median duration of treatment was 7.1 months (range 0.7–34.4), and at the time of data cutoff, six patients (12%) were still on treatment. 48 patients were assessable for tumor response. 19 patients (39.6, 90% CI 27.7–52.5) had an objective response, all of which were partial responses. Grade 3 drug-related adverse events were common, most frequently hand and foot skin reaction (16 patients, 33%), diarrhea (5 patients, 10%), renal failure (5 patients, 10%), fatigue (4 patients, 8%), and hypertension (3 patients, 6%). Two patients had grade four treatment-related adverse events: two cardiac ischemia or infarction, one hypomagnesaemia, and one chest or thorax pain. Four patients died during study treatment or within 30 days of the last dose. Two of these deaths were regarded likely to be related to the study drug. In summary, based on this phase II trial, the efficacy of Regorafenib in the first-line setting of unresectable RCC appears comparable to that of other targeted first-line drugs. However, testing Regorafenib in standard phase III trials seems inappropriate in view of its toxic effects.

3.5 Regorafenib in Soft-Tissue Sarcoma (STS)

The randomized phase II REGOSARC trial examined safety and efficacy of regorafenib in patients with advanced soft-tissue sarcoma (Mir et al. 2016). 182 patients who had previously received doxorubicin or other anthracyclines for soft-tissue sarcoma were randomized into four cohorts—liposarcoma, leiomyosarcoma, synovial sarcoma, and other sarcomas. Participants received either Regorafenib (R) or placebo (P). In the latter group, there was an optional crossover in case of centrally confirmed disease progression. Progression-free survival (PFS) was the primary endpoint. PFS for R versus P, respectively, was in the liposarcoma cohort 1.1 months versus 1.7 months, in the leiomyosarcoma cohort 3.7 months versus 1.8 months (HR 0.46, $p = 0.0045$), in the synovial sarcoma cohort 5.6 months versus 1.0 months (HR 0.10, $p < 0.0001$), and in the other sarcoma cohort 2.9 months versus 1.0 months (HR 0.46, $p = 0.0061$). Grade ≥ 3 side effects more frequent in the R group before crossover were arterial hypertension, foot skin reaction, and asthenia. There was one treatment-related death in the R group due to liver failure. Taken together, Regorafenib has a relevant antitumor effect in non-adipocytic soft-tissue sarcomas by improving PFS (Mir et al. 2016).

4 Detailed Analysis of Toxicity

4.1 Dermatological Toxicity

In the CORRECT trial (Grothey et al. 2013) (mCRC, 760 patients), Regorafenib caused adverse reactions involving the skin and subcutaneous tissues (72% vs. 24%) including hand–foot skin reaction (HFSR) and severe rash requiring dose modification. Serious adverse skin reactions including erythema multiforme (0.2% vs. 0%) and Stevens–Johnson syndrome (0.2% vs. 0%) were more frequent in Regorafenib-treated patients. Toxic epidermal necrolysis occurred in 0.17% of 1200 Regorafenib-treated patients across all clinical trials.

In a meta-analysis (Belum et al. 2013), 1078 patients treated with Regorafenib for mCRC, GIST, renal cell carcinoma (RCC), and hepatocellular carcinoma (HCC) were included. The overall incidence of all-grade and high-grade HFSR were 60.5 and 20.4%, respectively. The relative risk (RR) of all-grade and high-grade HFSR with Regorafenib compared to controls was increased for all-grade (RR = 5.4) and high-grade (RR = 41.99) HFSR. Interestingly, the incidence of HFSR varied significantly with tumor type ($p = 0.007$), and was 71.4% in RCC, 60.2% in GIST, 50.0% in HCC, and 46.6% in mCRC, respectively.

4.2 Hypertension, Cardiac Ischemia, and Infarction

In the CORRECT trial (Grothey et al. 2013) (mCRC, 760 patients), Regorafenib increased the incidence of hypertension (30% vs. 8%), myocardial ischemia, and infarction (1.2% vs. 0.4%).

4.3 Hepatotoxicity

In the CORRECT trial (Grothey et al. 2013) (mCRC, 760 patients), fatal hepatic failure occurred in 1.6% of patients in the Regorafenib arm and in 0.4% of patients in the placebo arm; all of the patients with hepatic failure had metastatic liver disease.

4.4 Gastrointestinal Perforation or Fistula

In the GRID trial (George et al. 2012) (GIST, 199 patients), 2.1% of Regorafenib-treated patients who were treated during the blinded or open-label portion of the study developed gastrointestinal fistula or perforation; two cases were fatal.

4.5 Hemorrhage

Regorafenib increased the incidence of hemorrhage in the CORRECT trial (Grothey et al. 2013) (mCRC, 760 patients). The overall incidence (CTC Grades 1–5) was 21% in Regorafenib-treated group compared to 8% in placebo group. Fatal hemorrhage occurred in 0.6% of Regorafenib-treated patients and involved the respiratory, gastrointestinal, or genitourinary tract.

4.6 Embryo–Fetal Toxicity

Regorafenib was found to be embryonic lethal and teratogenic in rats and rabbits at concentrations lower than those achieved in man at the recommended dose. Thus, the drug is likely to cause harm when administered during pregnancy.

5 Drug Interactions

5.1 Effect of Strong CYP3A4 Inducers

Co-administration of a strong CYP3A4 inducer (e.g., rifampicin, phenytoin, carbamazepine, phenobarbital, and St. John's Wort) together with Regorafenib decreased the mean exposure of Regorafenib, increased the mean exposure of the active metabolite M-5, and resulted in no change in the mean exposure of the active metabolite M-2. Thus, concomitant use should be avoided.

5.2 Effect of Strong CYP3A4 Inhibitors

Co-administration of a strong CYP3A4 inhibitor (e.g., clarithromycin, grapefruit juice, itraconazole, ketoconazole, posaconazole, telithromycin, and voriconazole) with Regorafenib increased the mean exposure to Regorafenib and decreased the mean exposure to the active metabolites M-2 and M-5. Thus, concomitant use should be avoided.

5.3 Effect of Regorafenib on UGT1A1 Substrates

Regorafenib and its metabolites (M-2 and M-5) competitively inhibit UGT1A9 and UGT1A1 at therapeutically relevant concentrations. Eleven patients received irinotecan-containing combination chemotherapy together with Regorafenib at a dose of 160 mg (Schultheis et al. 2013). The mean AUC of irinotecan is increased by 28% when irinotecan was administered 5 days after the final seven doses of Regorafenib.

6 Biomarkers

An analysis of plasma biomarkers and KRAS mutations in patients with mCRC treated with Regorafenib (Strumberg et al. 2012) (phase I study, 38 patients) revealed that during Regorafenib treatment VEGF plasma levels increased by 62.4% (change in arithmetic mean) and 95.6% at days 21 and 49, respectively. sVEGFR decreased by 35.8% (d 21) and 42.8% (d 49), respectively. KRAS mutations were detected in 53% of patients. Changes in VEGF and sVEGFR-2 did not correlate with PFS. Patients with mutated or wild-type KRAS were equally distributed among those who benefitted clinically (PFS $\geq$ 100 d). The observed changes in angiogenic plasma cytokines are supportive of the antiangiogenic activity of Regorafenib in patients with advanced CRC. The KRAS status was not predictive for a clinical benefit as determined by PFS. Recently, it has been suggested that in patients with Ras mutant CRC, a decay in Ras mutant clones as assessed by ctDNA after 8 weeks of treatment with Regorafenib and/or a decrease in the product of the median values of volume transfer constant and the enhancing fraction (KREF) as determined by dynamic contrast-enhanced (DCE) MRI prior to and at day 15, post-treatment can predict the duration of a response to regorafenib (Khan et al. 2017).

7 Summary and Perspectives

Regorafenib is an orally active multi-kinase inhibitor that is fairly well tolerated as a single agent in the clinical setting as judged by the available data from phase I, II, and III trials. The toxicity profile is comparable to other oral multi-kinase inhibitors with similar targets. Regorafenib has promising antineoplastic activity in several tumor entities. Three large, randomized phase III studies in patients with "difficult to treat" clinical settings, advanced mGIST, advanced mCRC, and advanced HCC, have shown a benefit for Regorafenib treatment regarding overall survival (CRC, HCC) and progression-free survival (GIST, CRC, and HCC). Consequently, Regorafenib as single-agent treatment has been approved by the FDA for the palliative last-line situation in mCRC, mGIST, and HCC. Further, clinical development of Regorafenib as a single agent or in combination with standard chemotherapeutic agents in various malignant tumors is ongoing.

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